The synthesis and photochemistry of some nitrogen heterocycles.

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THE SYNTHESIS AND PHOTOCHEMISTRY OF SOME NITROGEN HETEROCYCLES

Submitted by Michael Hutchins
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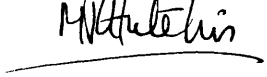
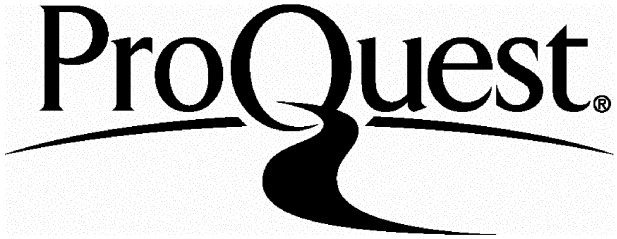
1983





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SUMMARY

The work described in this thesis was carried out between October, 1979 and September, 1982.

Several areas of chemistry have been covered and, despite the fact that there are some common factors linking them, it has been found most convenient to classify the work under two broad headings.

The first three chapters describe an investigation into the low potential anodic cyclisation of laudanosine to *O*-methylflavinantine. This reaction has previously been studied comprehensively by Miller[2] who has proposed a rather unusual mechanism to account for certain features of the cyclisation.

Chapter 3 of this thesis describes the generation, by non-electrochemical means, of a key intermediate in Miller's proposed mechanism. This intermediate has been shown not to cyclise in the predicted manner and so, to explain our observations, a new mechanism for the low potential transformation of laudanosine to *O*-methyl-flavinantine has been put forward.

Chapters 4, 5 and 6 are concerned with the application of dienamide photocyclisations to the synthesis of polycyclic indole derivatives.

This technique has been used successfully to prepare a number of novel polycyclic indoles, some of which we expect to show anti-cancer activity.

The development of a new synthetic route to the anti-cancer active indolo[2,3-*c*]isoquinolines has also been attempted. As part of this work, it became necessary to investigate certain aspects of the chemistry of 2-aminoindoles. Our efforts towards a novel and efficient synthesis of these unstable compounds, *via* *N*-phenylsulphonyl-2-lithioindole, are therefore recorded.

CONTENTS

CHAPTER 1

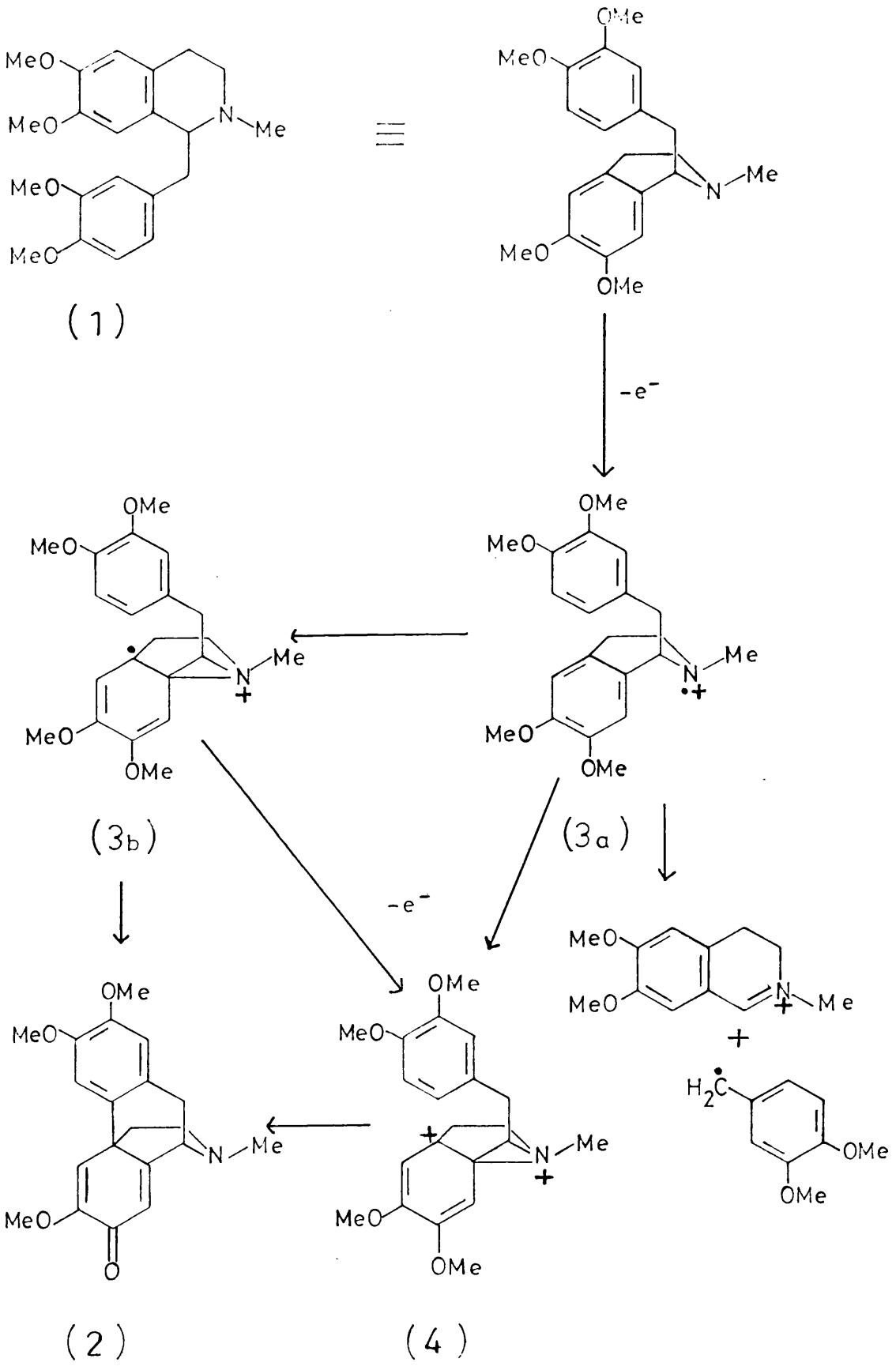
1.1 The electrochemical synthesis of *O*-methylflavinantine

In the past twenty years or so there has been a considerable upsurge of interest in methods of aryl-aryl bond formation.[1] Two synthetic techniques have emerged as being particularly useful in this respect. The first, photochemistry, and in particular the photocyclisation of the stilbenes, their aza-analogues and the related dienamides, is reviewed in Chapter 4 of this thesis. The other technique to have found widespread favour has been that of electrochemical or chemical coupling, particularly the former. Both anodic oxidative[2] aryl ring couplings and cathodic reductive syntheses[3] have been described in the literature and at Bath,[4] anodic oxidation has been used to synthesise a number of compounds which are otherwise rather inaccessible by conventional means. It is not the purpose of this introduction to provide a "state of the art" account of organic electrochemistry. Instead, initially, one particular reaction, a process of considerable synthetic potential, will be highlighted and its probable mechanisms discussed.

The anodic oxidation of laudanosine (1) in neutral solution ($CH_3CN/LiClO_4$) at +0.6 V (*vs.* S.C.E.) leads to the formation of *O*-methylflavinantine (2) in approximately 50% yield.[2(a-e)] If the electrolysis is carried out at *ca.* +1.1 V in acidic solution (HBF_4/CH_3CN) then the yield of (2) is increased to >90%.

Cyclic voltammetric studies of amines, such as triethylamine, have shown that, at approximately +0.6 V, anodic oxidation results in the loss of one electron from the lone pair on the nitrogen to form the aminium ion or radical cation, and it seems likely that the anodic coupling of laudanosine at the lower potential involves such an intermediate.

Miller has proposed a mechanism (see Scheme 1) in which anchimeric assistance or homoconjugation between the nitrogen and the ring is invoked, not only to explain why coupling occurs at the lower potential, but also to explain the regiospecificity of the reaction.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OMe
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OMe
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Me
MeO
O
(2)
OMe
MeO
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Me
MeO
OMe
(4)

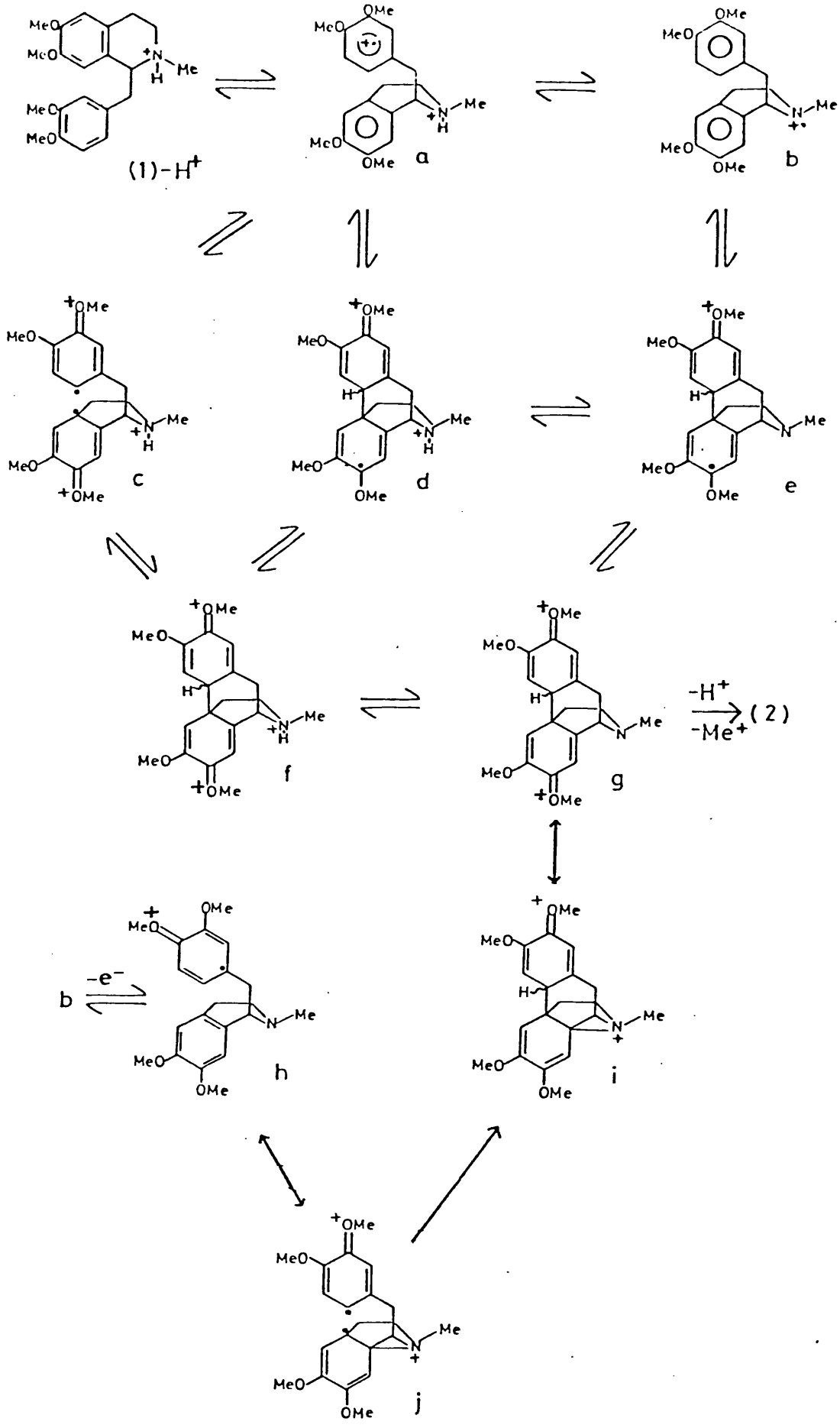
Scheme 1

Compounds where *N*-methyl has been replaced by a methylene group or an oxygen atom have similarly been subjected to electrolysis, but in these instances coupling has been observed to occur at both carbon atoms on the AB ring junction.[3f] It is not clear whether the coupling of laudanosine occurs *via* the radical cation (3) or whether further oxidation to the dication (4) takes place before coupling.

The lower yields of the morphinan derivative at +0.6 V have been attributed to decomposition of the radical cation through *C*-debenzylation as shown in Scheme 1.

At +1.1 V the picture is more complicated. In acid solution, cyclic voltammetric analysis shows that oxidation of the amine function does not occur to a measurable extent and that initial electron loss must therefore take place from the dimethoxylated aromatic rings. It is clear that cyclisation at +1.1 V takes place through an intermediate different from that implicated in cyclisation at the lower potential. However, this process is still regiospecific, a fact that Miller explains by suggesting that the amine function may still participate in the reaction in some way, although he does not elaborate upon this point.

The main complication, though, remains the possibility that coupling may occur *via* either a radical cation or a diradical dication. Evidence obtained by Miller in a detailed study[3g] of the reaction is apparently consistent with a number of mechanisms. These possibilities are reproduced in Scheme 2. The route a-d-e-g has been proposed as the most probable one; *i.e.*, loss of one electron at the anode followed by coupling, deprotonation and then further oxidation. The second oxidation is assumed, on the basis of kinetic data, to be a rate limiting step involving disproportionation of two radical cationic species in solution. This proposal is surely contradicted by the fact that the cyclic voltammagram of laudanosine in acid solution shows a <u>two electron</u> irreversible peak at +1.1 V, which supports the mechanism involving formation of the diradical dication as demonstrated in the cyclisations of other bi-aryl systems.

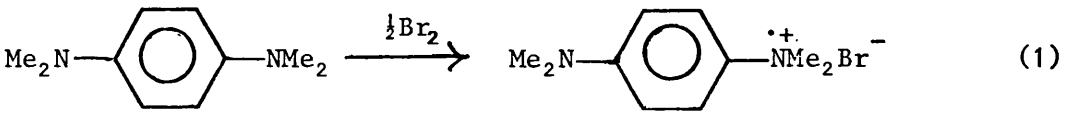


Scheme 2

Much of the uncertainty surrounding the mechanism of this reaction would be dispelled if one or more of the proposed radical and ionic intermediates could be produced unambiguously by an unrelated process. For example, if the radical cationic species (3) could be formed, then the argument as to whether coupling of this species takes place, or whether further oxidation must occur first, could be resolved.

1.2 Aminium ions

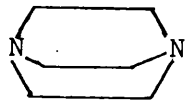
The nitrogen radical cation or aminium ion is a well documented species and reactions involving its intermediacy, although possibly not recognised as such at the time, have been known since the late nineteenth century.[5] Early examples include the so called Würster salts[6] which are salts consisting of an aromatic aminium ion and a non radical counter ion. For instance, mono-oxidation of *N*,*N*,*N'*,*N'*-tetramethyl-*p*-phenylenediamine (5) with bromine gives the aminium salt Würsters blue [equation (1)].



(5) (1)

The aromatic aminium ions show quite considerable stability as a result of the conjugation of the radical centre with the aryl ring. Charge transfer complexes such as those involving 1,6-diaminopyrene (DAP) and tetracyanoquinodimethane (TCNQ),[7] formally composed of an aminium ion and a radical cation, have been found to be exceptionally stable and can be analysed quite readily by conventional spectroscopic methods. Such complexes have attracted widespread interest as non ionic solid state conductors.

Alkyl aminium ions are predictably less stable; due not only to the lack of aromatic conjugative stabilisation, but also to the possibility of side reactions involving the neighbouring methylene groups. Of the known alkyl amino radical cations, the one derived from triethylenediamine (6) is noteworthy in that it has a lifetime of seconds; the relative stability being a result of the interaction of the two sets of lone pair electrons.[8]



(6)

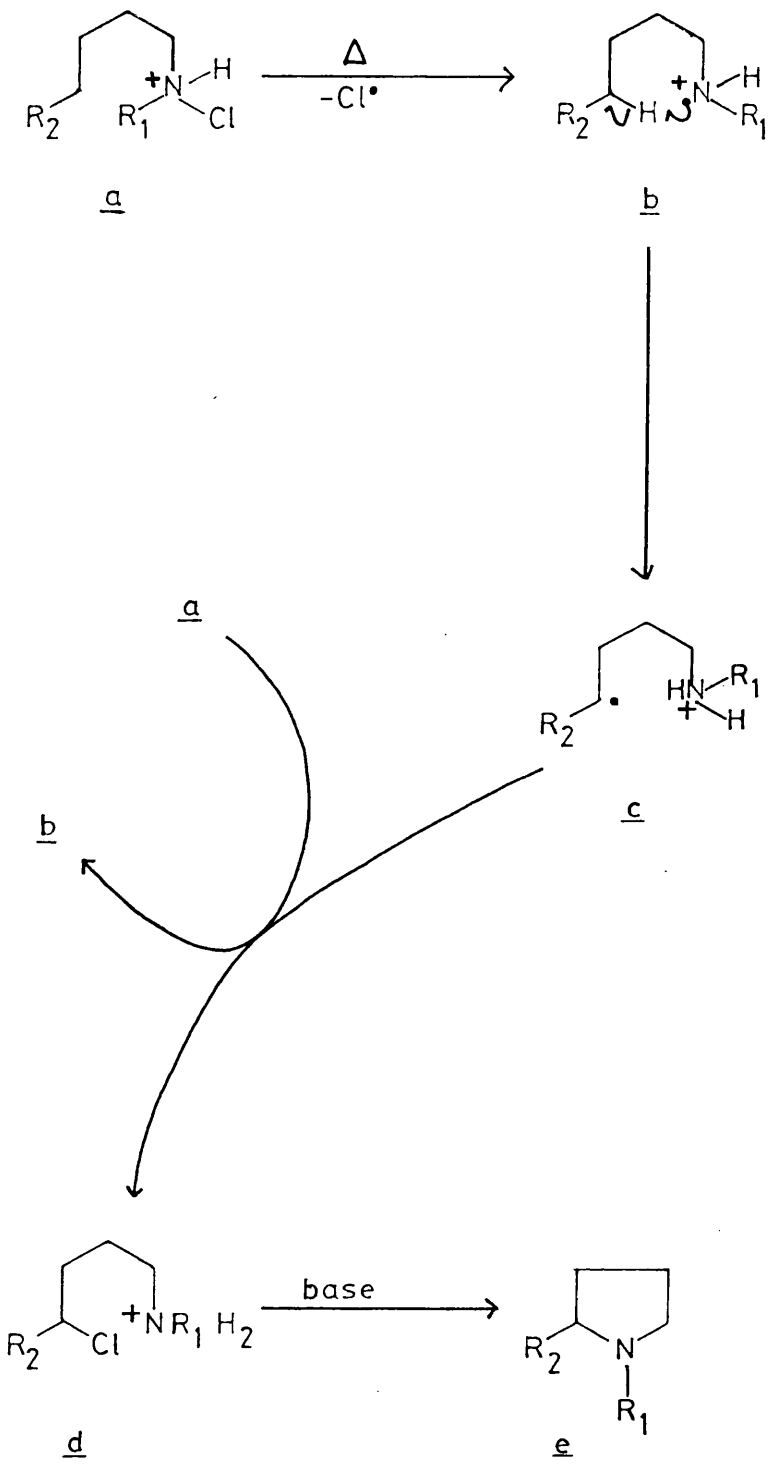
Probably the most widely studied process involving the nitrogen radical cation has been the Hoffman-Löffler-Freytag reaction.[5b,9] It was discovered that heating suitably substituted alkylchloramines in acid solution resulted in the formation of pyrrolidines. This reaction has since been used to prepare a large number of multicyclic amines which would otherwise have been synthesised only with difficulty. It is now accepted that the Hoffman-Löffler-Freytag reaction proceeds in the following way (Scheme 3).

The free radical chain mechanism of the reaction was proposed after observation that either u.v. irradiation or, in the absence of light, addition of a trace of the known radical initiator hydrogen peroxide, led to enhancement of the yields.

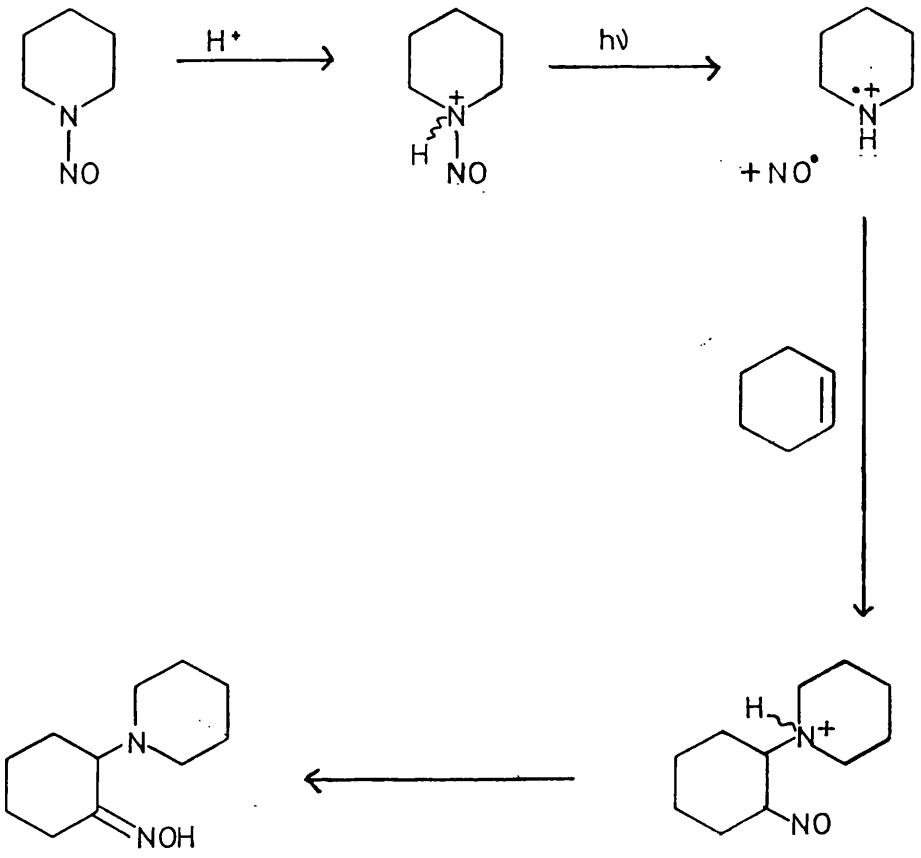
The chain propagating step is thought to be interaction of the radical ion *c* with the protonated chloramine *a*. Chlorosubstitution generally occurs at the δ-position reflecting the preference for a six-membered transition state.

Aminium ions may also be produced by transition metal reduction of haloamines, usually in the presence of acid. Once formed they may undergo a number of reactions. Reduction to the amine occurs fairly readily under both photo-reducing and chemical conditions, but a more facile process is the addition of the radical cation to multiple bonds. *N*-Chloramines add in good yields to dienes, to give the 1,4-adduct, and to halogenated olefins. The addition to alkyl olefins, allenes and acetylenes is less efficient and the Hoffman-Löffler-Freytag reaction and electrophilic chlorination become important side reactions with these compounds.

In an analogous process, *N*-nitrosamines can be persuaded to add to double bonds when photolysed in acid solution and here again the reactive intermediate is the aminium ion (Scheme 4).[10] It has been observed that irradiation of a methanolic solution of *N*-nitrosopiperidine in the



Scheme 3



Scheme 4

absence of an olefin results in photoreduction to give unsubstituted piperidine as one of the products. If an olefin such as cyclohexene is present, the degree of photoreduction of the radical cation is negligible and indeed, kinetic studies have shown that the rate of addition to alkenes is 5×10^3 as fast as photoreduction.

Chow has carried out flash photolysis studies which have established that the radical cation intermediate arises through either $n \rightarrow \pi^*$ or $\pi \rightarrow \pi^*$ absorption followed by fission of the N-N bond whilst the molecule is at the first excited singlet state. The latter conclusion was drawn as a result of experiments carried out with known triplet

sensitisers. Addition to double bonds is a stepwise radical process. This is evident from the fact that the photoaddition of *N*-nitroso-piperidine to both *trans*- and *cis*-2-butene gives the same mixture of *erythro* and *threo* adducts.

Hydrazines oxidise very readily to give radical cations.[5b] Such oxidations, which may be carried out using ceric ion, lead to a variety of products. Hydrazine itself forms di-imide by rapid deprotonation and further oxidation, 1,2-disubstituted hydrazines give rise to azo compounds and 1,1-disubstituted hydrazines yield 2-tetrazenes or hydrocarbons and nitrogen.

Aminium ions are also readily formed from hydrazines simply by treatment with acid. For example, the reaction of tetraphenylhydrazine is thought to proceed as follows (Scheme 5):

$$Ph_2N\text{-}NPh_2 + H^+ \longrightarrow Ph_2N\text{-}\overset{+}{N}HPh_2 \xrightarrow{H^+} 2Ph_2\overset{+\bullet}{N}H$$

$$Ph_2\overset{+\bullet}{N}H + Ph_2N\text{-}NPh_2 \longrightarrow Ph_2NH + (Ph_2N\text{-}NPh_2)^{+\bullet}$$

Scheme 5

More interestingly, perhaps, methylation of tetramethyl-2-tetrazene yields the pentamethyltetrazenium salt.[11] This salt decomposes slowly at room temperature and rapidly in aqueous solution at 0° C. It has been proposed that the decomposition occurs *via* the trimethylamine radical cation (Scheme 6).

$$Me_3\overset{+}{N}\text{-}N{=}N\text{-}NMe_2I^- \xrightarrow{H_2O} Me_3N^{+\bullet}I^- + N_2 + {}^{\bullet}NMe_2$$

$$Me_3N^{+\bullet}I^- \longrightarrow Me_3N + I^{\bullet}$$

$$2I^{\bullet} \rightarrow I_2$$

$$2\,{}^{\bullet}NMe_2 \rightarrow Me_2N\text{-}NMe_2 \text{ or } Me_2NH + CH_2{=}N\text{-}Me$$

$$2Me_2N\text{-}NMe_2 + I_2 \longrightarrow 2Me_2\overset{+\bullet}{N}\text{-}NMe_2 + 2I^-$$

Scheme 6

1.2.1 Aminating agents

A convenient method of generating hydrazines and hence, by implication, aminium ions is through the reaction of amines with a suitable aminating agent. Chapter 2 describes such a process. Further examples of the use of aminating agents, in this case for *C*-amination, are reported in Chapter 5. It is therefore pertinent at this point to consider the properties and reactions of aminating agents and the further reactions of *N*-aminated compounds.

The use of aminating agents for direct introduction of an amino group into a molecule is a technique which has found widespread application. While a complete survey of aminating reagents is outside the scope of this thesis, it will be useful to consider further a number of the more important members of this class of compound and, in particular, those which act by electrophilic attack of the reagent upon the molecule. Such reagents, which may be considered sources of the "NH_2^+" species, have the general formula NR_2X where X may form a stable anion. Falling into this category are the substituted hydroxylamines and the halogenated amines of which chloramine[9b] is the simplest example. Haloamines, which have attracted considerable interest, are primarily reagents for the amination of carbon centres. The Hoffman-Löffler-Freytag process, which may be formally considered as an intramolecular amination, and the related addition of haloamines to multiple bonds, are radical reactions. However, the haloamines act in an ionic electrophilic sense in their reactions with anions[13] and certain aryl ring systems[14] [equations (2)-(8) are representative examples].

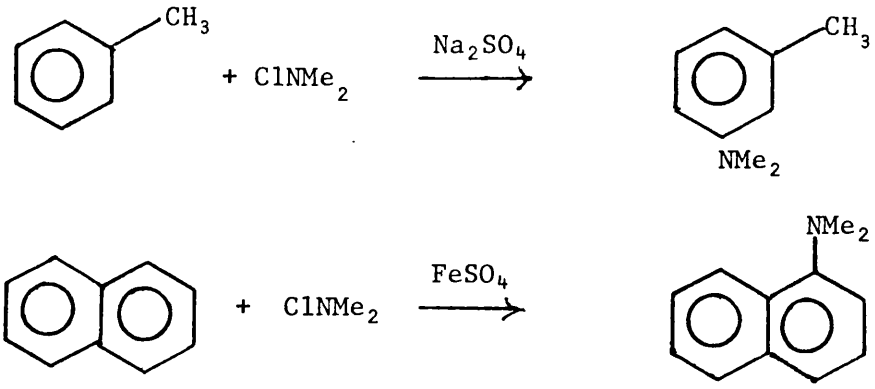
$$C_2H_5MgCl + NH_2Cl \longrightarrow C_2H_5NH_2 \quad (57.2\%) \qquad (2)$$

$$PhMgCl + NH_2Cl \longrightarrow PhNH_2 \quad (26.7\%) \qquad (3)$$

$$PhCH_2MgCl + NH_2Cl \longrightarrow PhCH_2NH_2 \quad (85\%) \qquad (4)$$

$$n\text{-}Bu_2Mg + NH_2Cl \longrightarrow n\text{-}BuNH_2 \quad (90\%) \qquad (5)$$

$$C_6H_6 + ClNMe_2 \longrightarrow PhNMe_2 \quad (56\%) \qquad (6)$$



The scope of the reaction of haloamines with Grignard reagents was determined by Coleman[13] who found that the most fruitful reactions were those between organometallics of the type R_2Mg and chloramine itself. Interestingly, the phenyl Grignard reagents gave very low yields of amines upon treatment with haloamines.

Although examples of *N*-amination with chloramines are known, they are not the reagents of choice for the amination of nitrogen centres. In the case of pyridine, for instance, treatment with chloramine results in the formation of a low yield of 2-aminopyridine rather than the *N*-aminopyridinium species.[15]

1.2.2 Hydroxylamine based aminating agents

N-Aminations are efficiently carried out using the *O*-substituted hydroxylamines of which mesitylenesulphonylhydroxylamine (MSH)[16] and hydroxylamine-*O*-sulphonic acid (HOSA)[17a] have been used most widely. Other reagents, *e.g.*, *O*-[2,4-dinitrophenyl]hydroxylamine[18] have been reported, but have found fewer applications than MSH and HOSA.

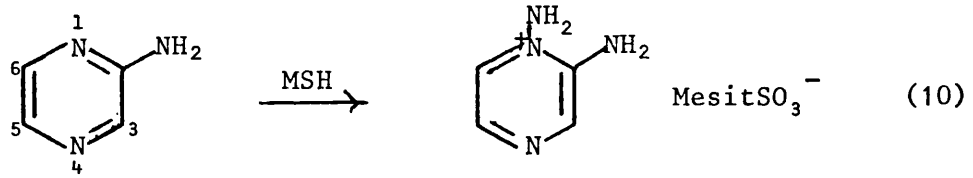
MSH, despite its tedious preparation, is the most versatile reagent due to its ready solubility in organic solvents and its superior aminating power. The scope of the amination reaction with MSH is comparable to that of *N*-oxide formation.[19] In contrast, HOSA is easier to prepare [equation (9)], but can only be used in very polar

$$(\overset{+}{N}H_3OH)_2SO_4^{2-} + 2H_2SO_4.SO_3 \longrightarrow 2\overset{+}{N}H_3O\bar{S}O_3 + 3H_2SO_4 \qquad (9)$$

solvents such as water, diglyme or methanol. In addition, it fails to

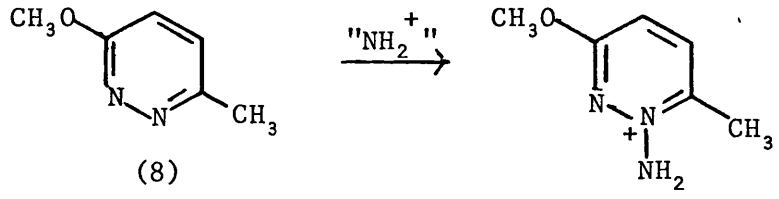
aminate a number of heterocycles and with others anomalous products are formed. For example, pyrimidine is not *N*-aminated by HOSA, but instead forms only the *N*-oxide.[20] Pyridines bearing electron withdrawing groups such as CN, CO_2R and $CONH_2$ are also unreactive towards HOSA.[21]

The reactivity of MSH is such that when faced with a number of possible amination sites, reaction will take place at the most basic nitrogen. Thus 2-aminopyrazine (7) is aminated regiospecifically at the 1-position [equation (10)].[22]



(7) (10)

Amination of 3-methoxy-5-methylpyridazine (8) also takes place exclusively at the 1-position. It appears that the positive inductive effect of the methyl group takes precedence over the net effect of the methoxyl. Presumably in this case, the lone pair donating ability of the oxygen is outweighed by its electronegativity, since it seems unlikely that the regiospecificity can be explained on steric grounds alone.

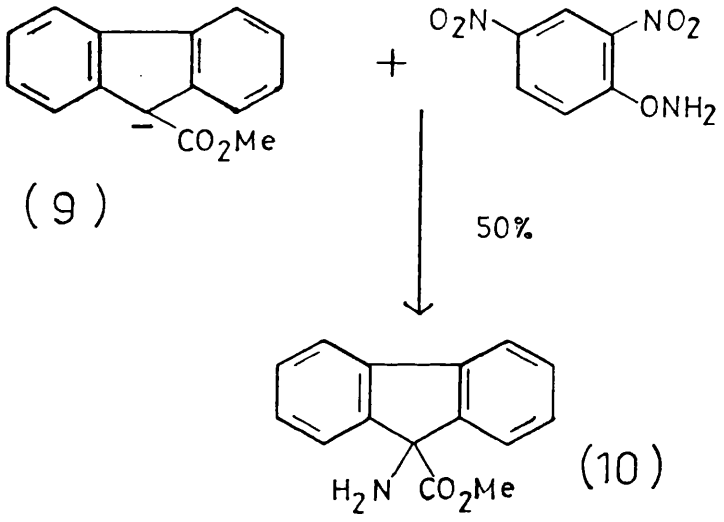


(8) (11)

1.2.3 *C*-Amination

Apart from the amination of relatively simple Grignard reagents described by Coleman, the direct introduction of an amino function at carbon centres has posed many problems for organic chemists.

Sheradsky has described the amination of the anion of fluorene-9-carboxylic acid methyl ester (9) to give a moderate yield of the α-amino compound [(10), equation (12)] and has also reported the successful amination of a number of substituted malonic ester carbanions.[23] The importance of this particular procedure lies in the fact that hydrolysis and decarboxylation of the products leads to the α-amino acids. Oguri[24] has synthesised amino acids directly by reaction of carboxylate dianions with a suitable aminating agent [equation (13)].



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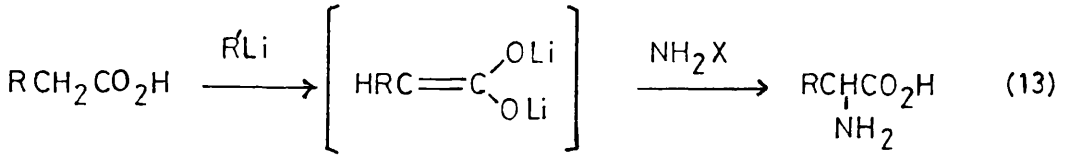


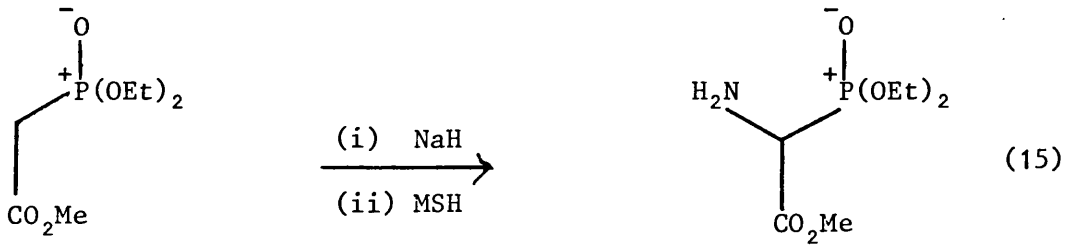
(13)

A number of reagents were examined in this study and yields of the amino acids were variable. Attempts by Gilmore and Lin[25] to form sulphonic acid analogues of α-amino acids by amination of the sulphonamide α-carbanion failed, although several aminating agents were used [equation (14)]. However, Scopes[26] has reported that the

$$RCH_2\text{-}SO_2NH_2 \xrightarrow[(ii)\ NH_2X]{(i)\ n\text{-BuLi}} RCH(NH_2)\text{-}SO_2NH_2 \qquad (14)$$

X = Cl, 2,4-dinitrophenolate, mesitylenesulphonate, CH_3O

phosphorus stabilised carbanion (11) can be successfully aminated by MSH to yield (12), an important cephalosporin precursor, in reasonable yield [equation (15)]. The problems, and in particular the low yields,

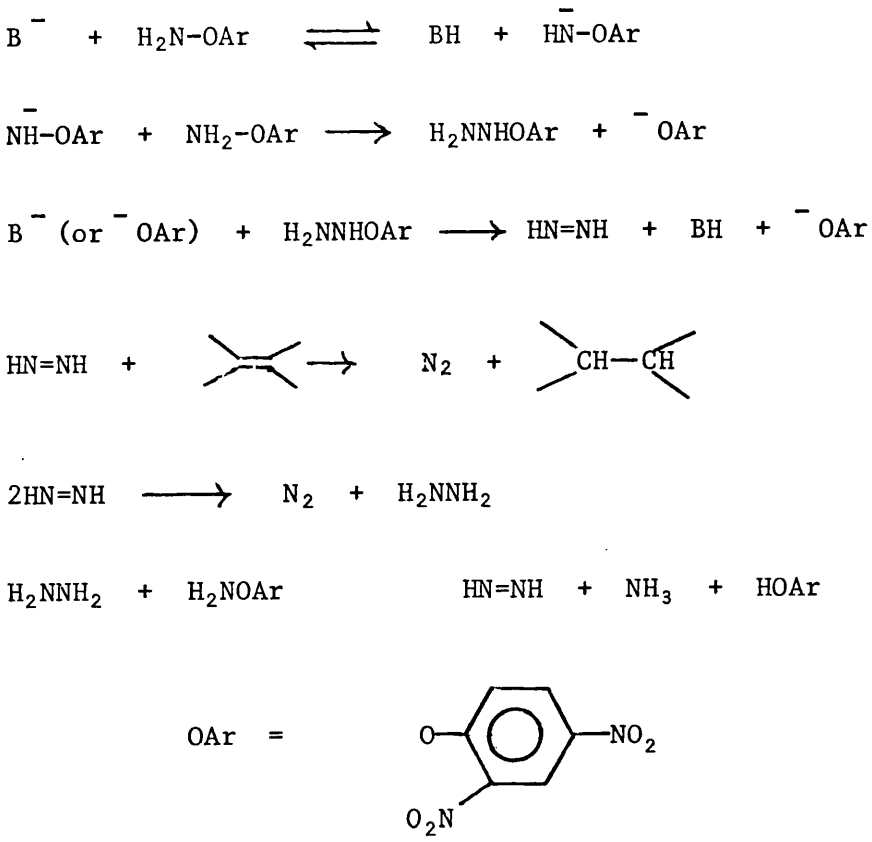


(15)

(11) (12)

associated with the amination of carbanions have been partly explained by Loudon[27] who treated a number of anions of varying basicity with *O*-[2,4-dinitrophenyl]hydroxylamine. It was found that the fairly well stabilised malonate derived anions, *e.g.*, $Ph\bar{C}(CO_2Et)_2$, were aminated in reasonable yields, whereas with less well stabilised species *e.g.*, Ph-$\bar{C}$H-CN, the degree of amination was considerably lower. In all cases 2,4-dinitrophenol was isolated and in cases where yields were low, the addition of alkenes to the reaction mixture resulted in their reduction to the alkanes. From these facts it was concluded that base catalysed breakdown of the reagent was taking place and that this process involved the intermediacy of the reducing agent di-imide (Scheme 7).

It appears that stabilised carbanions such as the malonates and methyldiethylphosphonoacetate are barely basic enough to deprotonate the N-H function although, even in these cases, the yields are far from quantitative. The lower yields associated with less stabilised carbanions



Scheme 7

such as lithiophenylacetonitrile indicate that these are borderline cases where deprotonation and subsequent reagent breakdown is a serious competitor to amination.

Oguri[28] and his co-workers have partly overcome this difficulty. It is evident that the presence of electron withdrawing groups, such as 2,4-dinitrophenyl and mesitylenesulphonyl, attached to the hydroxylamine O-atom greatly enhances the acidity of the N-H bond. Oguri has therefore utilised hydroxylamines O-substituted with electron donating groups such as methyl, ethyl and isopropyl and, up to a point, amination proceeds in higher yields with a smaller degree of base catalysed reagent decomposition. However, the decreasing N-H acidity is accompanied by a decrease in the leaving ability of the -OR group and hence a reduction in aminating power. These two effects may be seen clearly in Table 1, with the best yield for the amination of isovaleric acid arising from the use of the aminating agent NH_2OMe.

Table 1

α-Amination of isovaleric acid

$$(CH_3)_2CHCH_2CO_2H \xrightarrow[(ii)\ NH_2X]{(i)\ LDA} (CH_3)_2CHCH(NH_2)-CO_2H$$

Aminating agent (X=)	Yield (%)
O-2,4-dinitrophenyloxy	0
OCH_3	33.9
OCH_2CH_3	22.4
$OCH(CH_3)_2$	25.4
$OC(CH_3)_3$	18.3
OCH_2Ph	trace
OSO_3H	trace
Cl	7.7
O-2,4,6-trimethylphenylcarboxy	4.3

The use of N-substituted hydroxylamine derivatives, *i.e.*, with no N-H linkages from which deprotonation can take place, should enable successful amination of organometallic species to take place. Such reagents would, however, have only a limited use. Boche[29] has treated a series of alkyl- and aryl-lithiums with *N*,*N*-dialkylmesitylene-sulphonylhydroxylamine and *N*,*N*-dialkylbenzenesulphonylhydroxylamine. Representative examples are shown below [equations (16)-(18)].

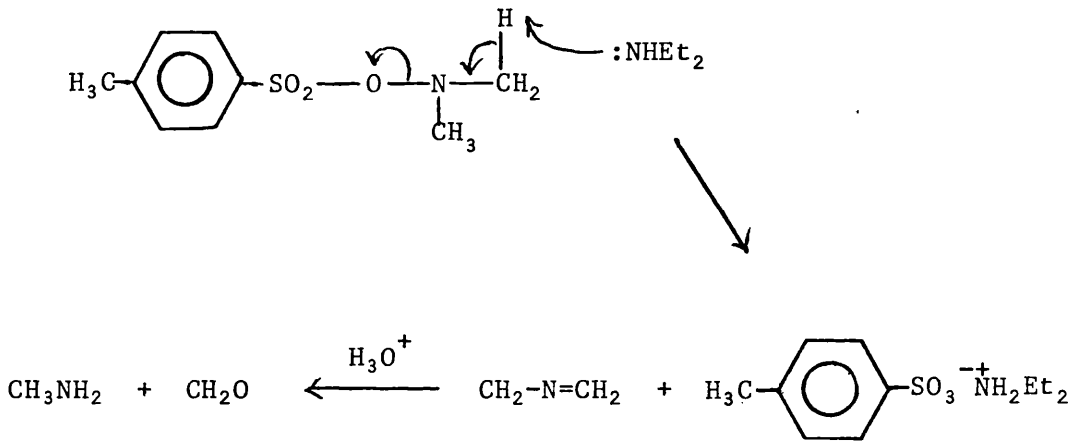
$$MeLi + ArSO_2ONMe_2 \longrightarrow MeNMe_2 \quad (45\%) \quad (16)$$

$$PhMgBr + ArSO_2ONMe_2 \longrightarrow PhNEt_2 \quad (42\%) \quad (17)$$

$$LiC(Ph)(CN)CO_2Et + ArSO_2ONMe_2 \longrightarrow Me_2NC(Ph)(CN)CO_2Et \quad (95\%) \quad (18)$$

Ar = 2,4,6-trimethylphenyl

It is significant that the best yield was obtained from the amination of the stabilised carbanion of ethyl-2-cyano-2-phenyl-acetate. This indicates that the stronger bases may be causing some decomposition of the reagent. A possible decomposition pathway is revealed in Barton's report[30] that treatment of *O*-tosyl-*N*,*N*-dimethyl-hydroxylamine with diethylamine results in decomposition of the reagent and the appearance of formaldehyde as a major side product. Barton has proposed that the base causes elimination of *p*-toluenesulphonic acid from the reagent (13) to give an intermediate imine which is subsequently hydrolysed to formaldehyde by acid treatment (Scheme 8).



Scheme 8

Barton has also reported, however, that the kinetically less basic Grignard reagents cyclohexyl and phenylmagnesium bromide can be aminated successfully in reasonable yields.

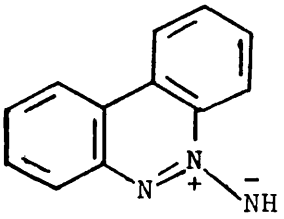
1.3 Properties and reactions of *N*-aminated compounds

1.3.1 General properties

N-Amination has been used as the starting point for the synthesis of a large number of heterocyclic compounds.[12a,17] Of the many examples of such syntheses, several types have assumed a particular

importance and these are dealt with briefly in following paragraphs.

Many of the further reactions of *N*-aminated heterocycles involve the betaine or *N*-imino ylid formed by treatment of the salt with base. The betaines are generally unstable species although benzo[*c*]cinnoline-*N*-imine (13) is isolable as a stable crystalline solid.[31]



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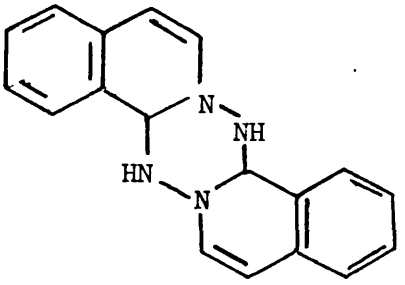
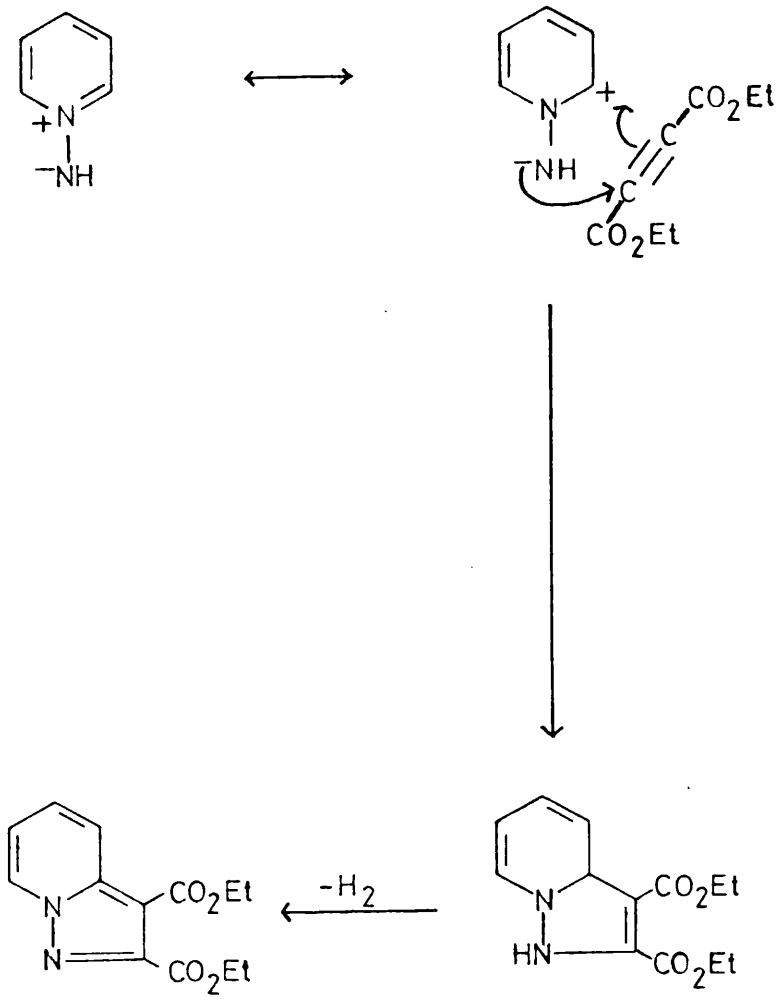


(14)

N-Imines are thought to exist in equilibrium with the dimerised species in solution[32] and the crystalline dimers of quinoline, isoquinoline (14) and phenanthridine have all been isolated.[33]

The basicity of the *N*-imines varies according to the nature of the substituent on the imino nitrogen. The pK_α values of pyridine unsubstituted imine have been quoted variously as 11.2[34] and 13.6[21] in different studies with the *N'*-methylimine[34] being assigned a pK_α of 12-13. The presence of electron withdrawing substituents predictably lowers the basicity; to a pK_α value of 3.2 in the case of pyridine- -benzoylimine[21] and 3.6 for the *N'*-acetylimine.[21] The strongly electron withdrawing nitro group lowers the pK_α still further to -4.6 in the *N*-nitroiminopyridine.[21]

The ability of pyridine-*N*-imine to act as a 1,3-dipole is well known, due largely to the efforts of Huisgen[35] and his co-workers. It has been found that pyridine-*N*-imine will undergo 1,3-dipolar addition to a wide variety of suitably activated multiple bonds of the type C=X or C≡Y where X and Y may be carbon atoms or heteroatoms. For example, addition to diethylacetylenedicarboxylate takes place to give the pyrazole (15) in good yield (Scheme 9).



Scheme 9

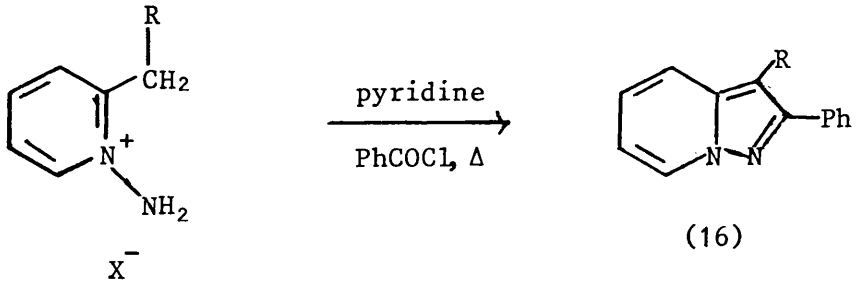
Addition to substrates such as nitriles and carbondisulphide gives rise to triazolo and thiadiazolopyridine derivatives respectively.

The u.v. irradiation of *N*-imino- and *N*-acylimino-pyridines leads to the formation of 1H-1,2-diazepines.[36] This reaction, which has been comprehensively studied by Streith and Snieckus among others, is thought to involve a diaziridine or 1,7-diazanorcaradiene intermediate (see Scheme 10), although such an intermediate has been neither isolated nor detected spectroscopically. Rearrangement probably takes place from the first singlet excited state which has been ascribed to the $\pi \rightarrow \pi^*$ transition. The use of triplet sensitisers such as eosin merely leads to N-N bond fission, a process which is only of minor importance in the absence of a sensitiser.

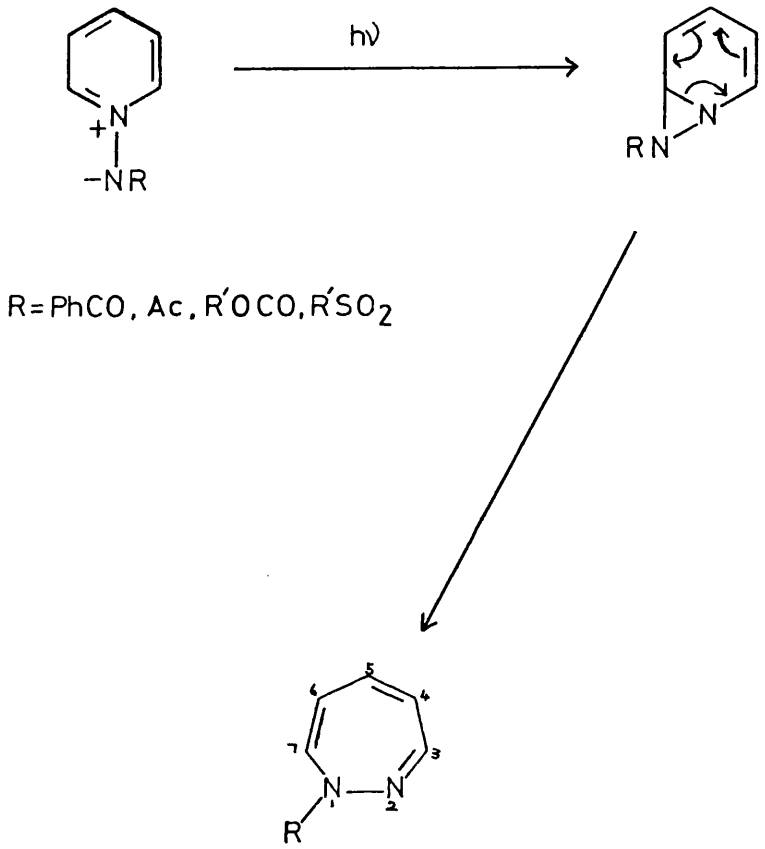
The reaction has been shown to be a general one and has been applied successfully to a variety of fused heterocyclic systems although, in some instances, ring expansion to a 1,3-diazepine or N-N bond fission of the diaziridine intermediate, leading to 2-amino derivatives, may occur instead.

1.3.2 The cyclisation of *N*-iminoheterocycles to fused pyrazoles or triazoles

Treatment of 2-alkyl-*N*-aminopyridinium salts with acylating agents such as acetyl chloride or benzoyl chloride in the presence of bases results in cyclisation to pyrazolo[1,5-*a*]pyridines [equation (19)].[37]



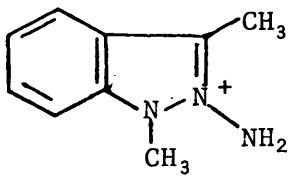
(16) (19)



Scheme 10

The reaction with acetyl chloride proceeds very rapidly, but the reported isolated yields are low (*ca.* 20%). The cyclisation with benzoyl chloride requires a much longer reaction time (24 h) and with shorter reaction times only the *N*-acylimino heterocycle is isolated. An added complication to the cyclisation of 2-methylpyridinium imines is that the initially formed 3-unsubstituted pyrazole [(16), R = H] is invariably further acylated to give the 3-acyl derivative [(16), R = R'CO].

This reaction is a general one and pyrazolodiazines,[20] pyrazolo-[5,1-*b*]thiazoles[38] and imidazo[1,2-*b*]pyrazoles[38] have all been synthesised in an analogous manner. Surprisingly the 1,3-dimethylindazolium salt (17) does not ring close under the same conditions, but instead rearranges to the 3-acylaminomethyl and acyloxymethyl derivatives [(18), R = OAc or NHAc].[39]



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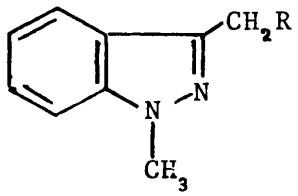
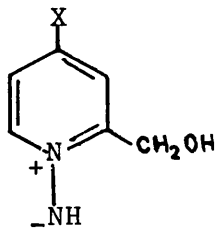


(18)

In a related process, 2-hydroxymethyl-*N*-imines (19), are cyclised under acylating conditions to give the 3-hydroxy- or acyloxy-pyrazolopyridines [(20), R = H or R'CO].[40]



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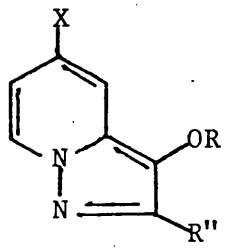
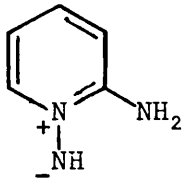


(20)

If 2-amino-*N*-imines are treated with acylating agents, *s*-triazolo fused heterocycles are formed. An example of this type of reaction is the formation of *s*-triazolo[1,5-*a*]pyridine (22) when 2-amino-*N*-iminopyridine is heated with formic acid in benzene.[41]



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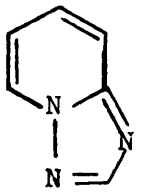
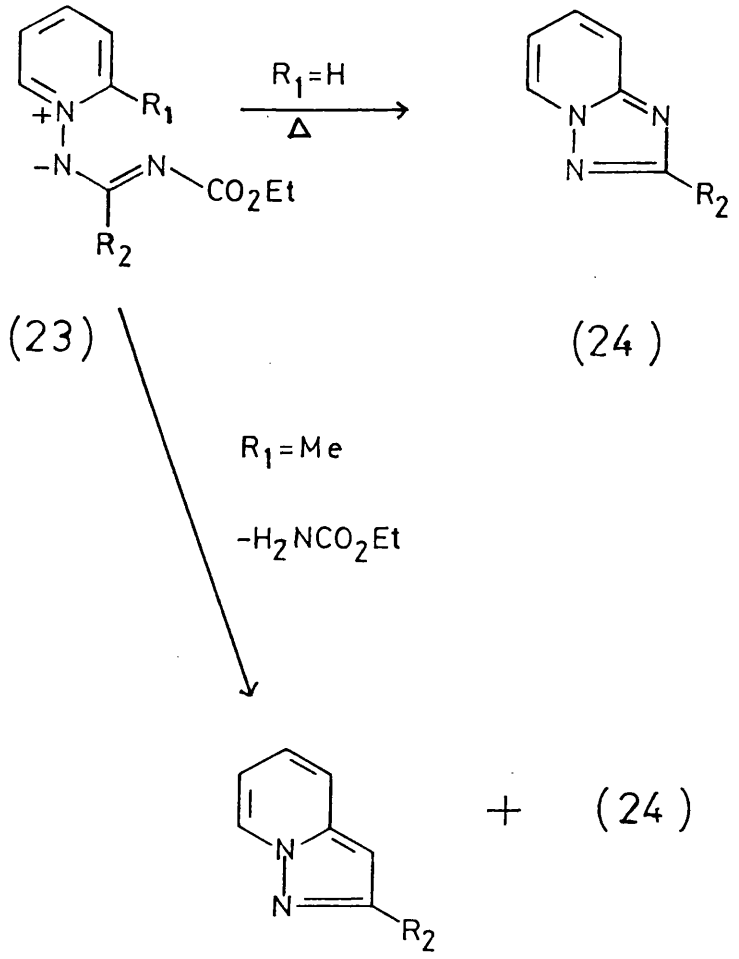


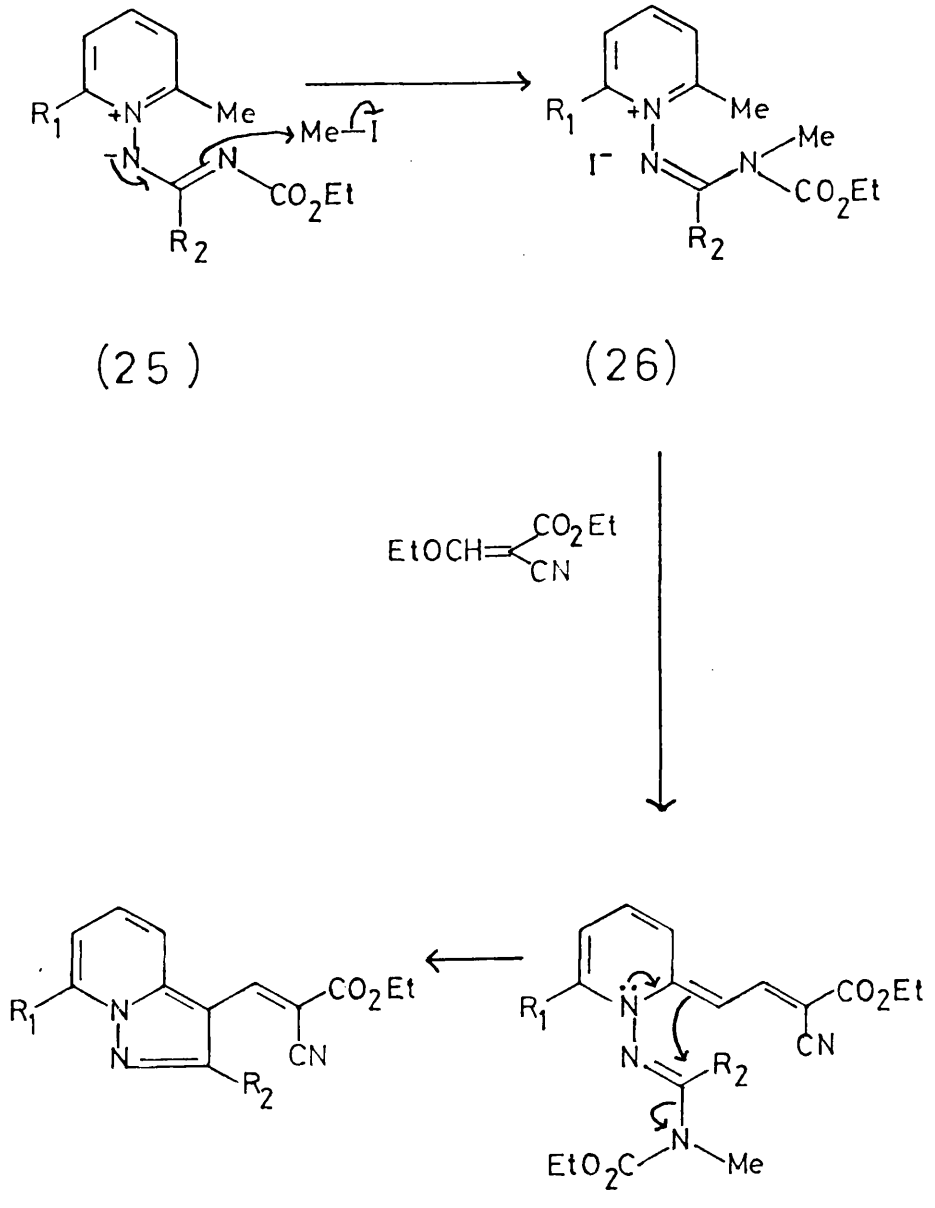
(22)

This synthesis has been extended to yield *s*-triazolo derivatives of the diazines, thiazoles, benzimidazoles and thiadiazoles.[42]

s-Triazolo[1,5-*a*]pyridines may also be synthesised through thermal cyclisation of *N*-imidoyliminopyridinium betaines [(23), Scheme 11]. When $R_1 = CH_3$, cyclisation to the pyrazole is a competing process.[43] Formation of the pyrazole is thought to proceed *via* initial deprotonation of the 2-methyl group to give the enamine. It therefore follows that if the molecule can be held in the enamine configuration, cyclisation to the pyrazole should be the predominant process. Kakehi has achieved this in his synthesis of pyrazolo[1,5-*a*]pyridines from allylidenedihydropyridines (Scheme 12).[44] Conversion to the tautomer from which cyclisation to the triazole takes place was prevented by methylation of the imidoyl nitrogen of the betaine (25). The allylidene function was then introduced by reacting the methiodide (26) with the activated ethoxymethylene copound (27) in the presence of base. Cyclisation of the resulting allylidenedihydropyridine (28) was usually accomplished simply by heating. In some cases, however, cyclisation was found to be so facile that isolation of the allylidenedihydropyridines in the preceding step proved to be impossible.



Scheme 11



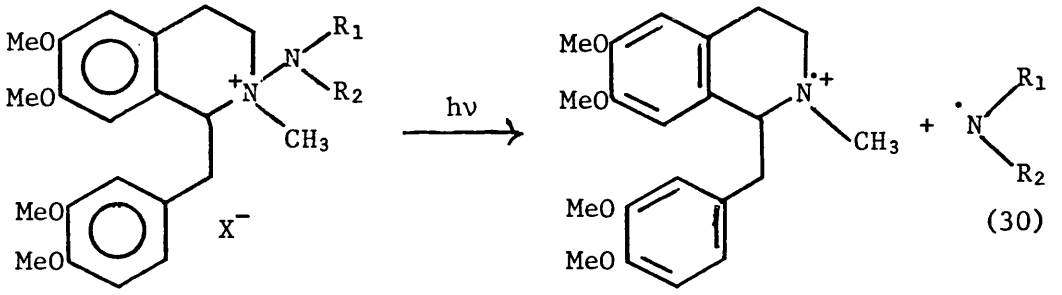
Scheme 12

CHAPTER 2

AN INVESTIGATION INTO THE ANODIC OXIDATIVE CYCLISATION OF LAUDANOSINE TO *O*-METHYLFLAVINANTINE

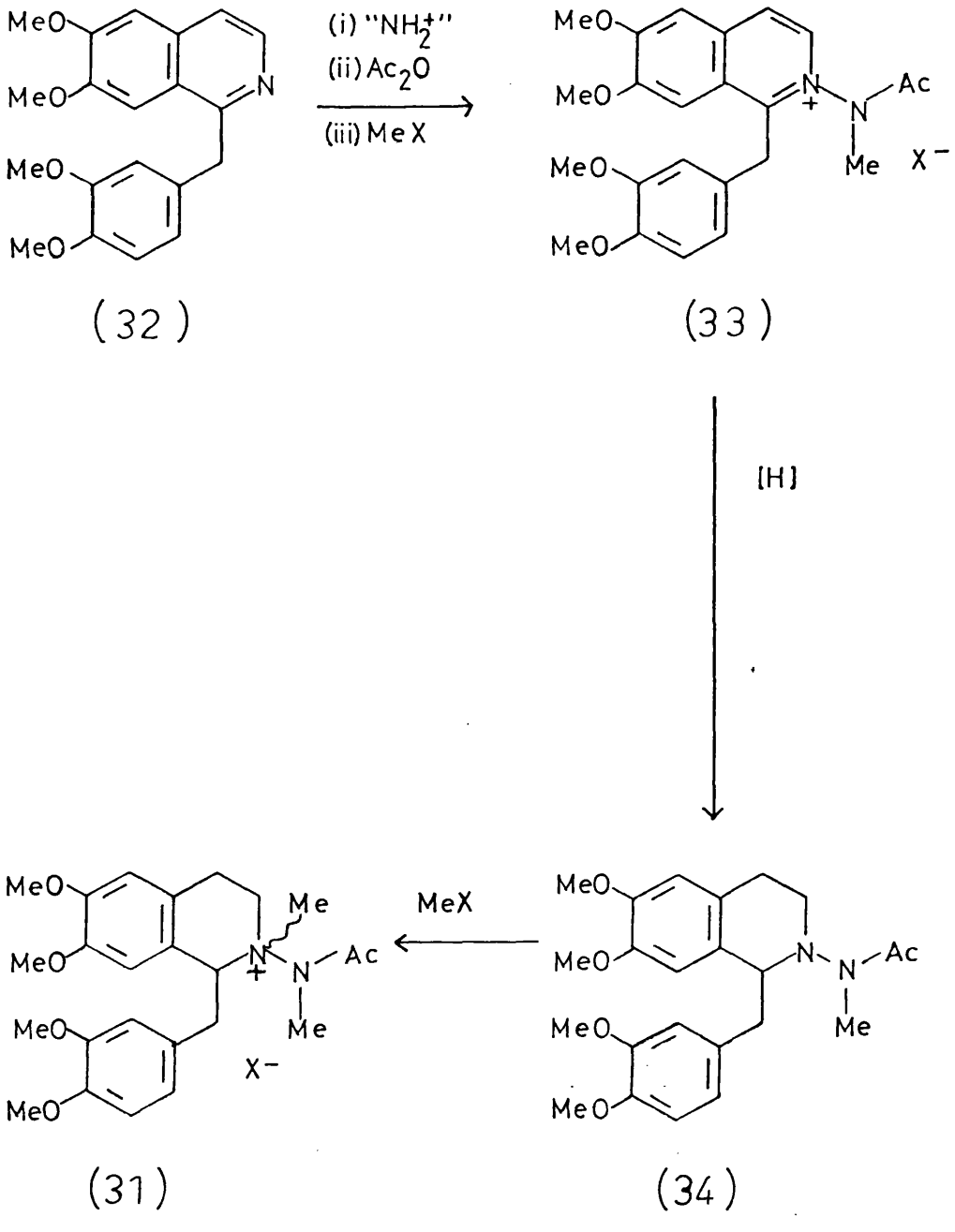
2.1 The preparation of 2-[*N'*-methylacetamido]-1,2,3,4-tetrahydropapaverine and its analogues

A survey of the reactions cited in the literature, in which the amininium radical species is involved, led us to the conclusion that the radical cationic species (3), postulated by Miller as an intermediate in the anodic cyclisation of laudanosine,[2] could be formed by homolytic cleavage of the N-N bond in compounds of the type (29), as shown in Scheme 13.



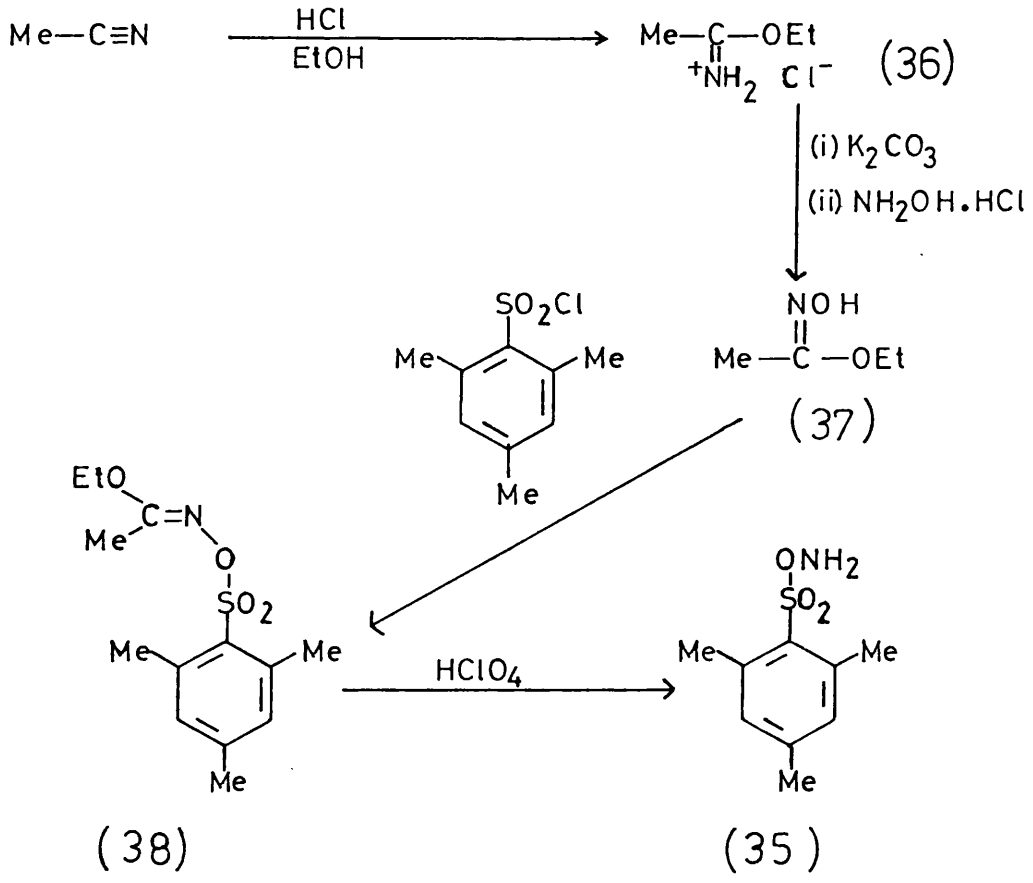
Scheme 13

There is ample precedent for this type of bond cleavage and examples of such processes have already been discussed in the preceding chapter. The substituent groups R_1 and R_2 on the departing nitrogen radical (30) may be chosen so as to enhance its stability and in our case the methylacetamide unit was selected. Our initial target molecule, therefore, was the quaternary salt (31). It was envisaged that this might be formed *via* an amination, acetylation, methylation sequence to give the methylacetamidoisoquinolinium species (33), followed by reduction to the tetrahydroisoquinoline and subsequent methylation with a suitable reagent (see Scheme 14). The amination, acetylation, methylation procedure is well known in pyridine chemistry[40,45] and has been used, for example, in the synthesis of pyrido[4,3-*b*]-carbazoles;[46] it generally takes place in good overall yield.



Scheme 14

Of the known aminating agents, hydroxylamine-*O*-sulphonic acid is by far the cheapest and most readily available, but as mentioned previously, it shows only a limited solubility in most organic solvents. Not surprisingly, we were unable to find a suitable common solvent for both reagent and substrate. A heterogeneous reaction in ethanol did not lead to any aminated product. Attention was therefore turned towards the less accessible, but by far superior aminating agent mesitylenesulphonylhydroxylamine (35). This reagent was made according to Tamura's method[47] (see Scheme 15). Accordingly,



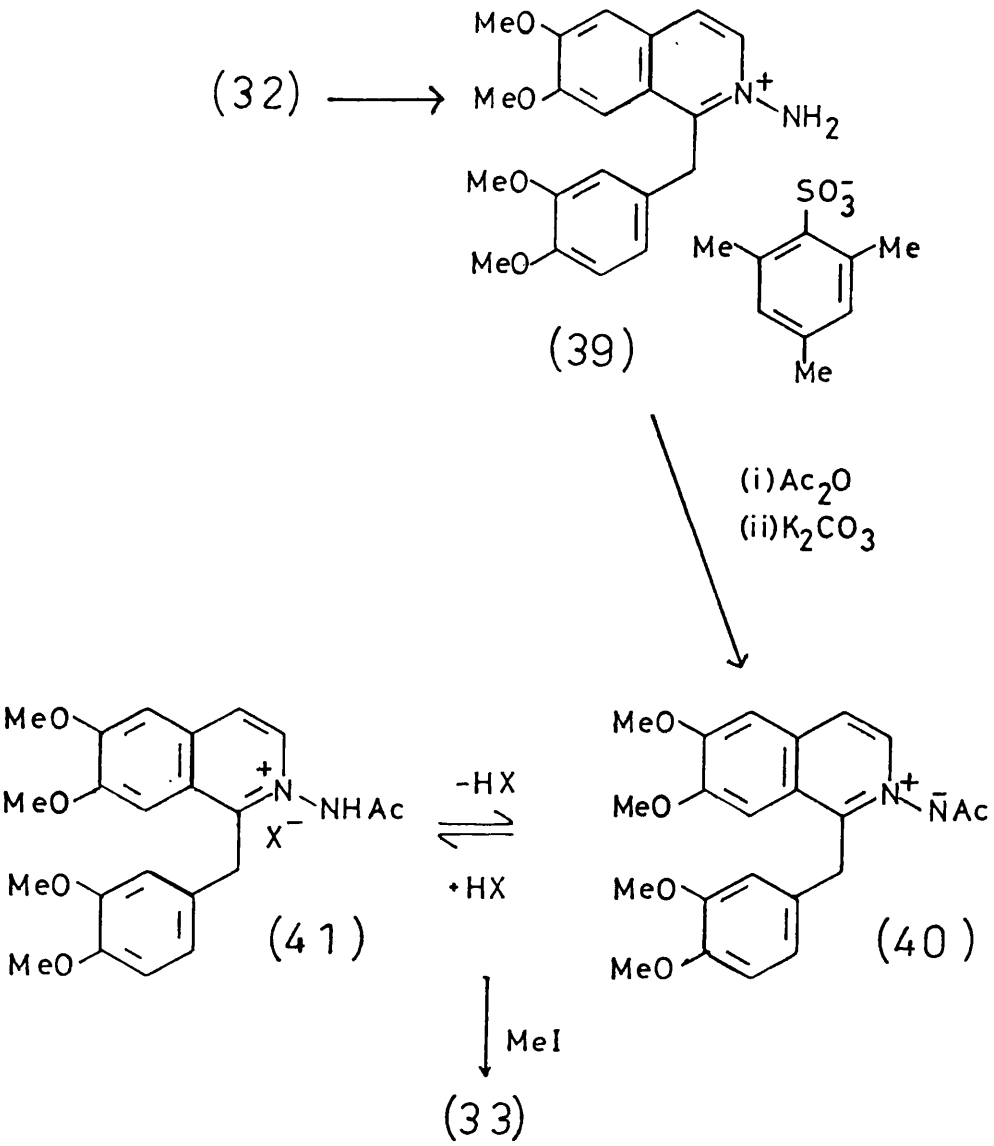
Scheme 15

hydrogen chloride was bubbled through an ethereal solution of ethanol and acetonitrile to give, after removal of the solvent, ethylacetimidate hydrochloride (36) as a colourless solid in 85% yield. Basification and treatment with hydroxylamine hydrochloride yielded the N-protected

1-ethoxy-1-oximidoethane (37), as a clear oil that crystallised into long needles when refrigerated. Reaction of the oxime with mesitylenesulphonyl chloride in dimethylformamide solution and subsequent work-up afforded 1-[*O*-mesitylenesulphonyloximido]-1-ethoxyethane (38) as a colourless solid which could be conveniently stored in the freezer until required. Removal of the protecting group from nitrogen to give mesitylenesulphonylhydroxylamine (35) was accomplished in yields of >50% using 62% perchloric acid. In view of the well known instability and explosive nature of MSH,[48] this final hydrolysis step was only carried out immediately prior to the use of the reagent.

The amination of papaverine (32) was readily achieved by addition of a slight excess of MSH to an ice cold solution of the alkaloid in dichloromethane. The resultant *N*-aminopapaverinium mesitylenesulphonate salt (39), which was precipitated from solution by the addition of ether, was obtained in yields of up to 90%. On occasions it was obtained as a colourless extremely hygroscopic solid, which formed a gum within minutes of exposure to moist air, but more usually it was obtained from solution as a gum which, upon prolonged exposure to air or trituration in ether, solidified to give the monohydrate. This could be recrystallised from ethanol. The presence of the water of crystallisation was indicated by the ^{1}H n.m.r. spectrum and the degree of hydration was also evident from the elemental composition obtained by microanalysis. Attempts to dry dichloromethane solutions of the reagent over molecular sieves prior to use, thereby ensuring formation of the anhydrous salt, resulted in partial decomposition of the reagent.

The amine was acetylated in cold aqueous ethanol with an excess of acetic anhydride. Decomposition of the excess reagent with sodium or potassium carbonate and extraction into dichloromethane yielded what was expected, in accordance with the observations of previous workers,[37,40,44,45] to be the ylide [(40), see Scheme 16]. However, ^{1}H n.m.r. analysis of the resulting orange meringue indicated the presence of the mesitylenesulphonyl entity and it therefore seems

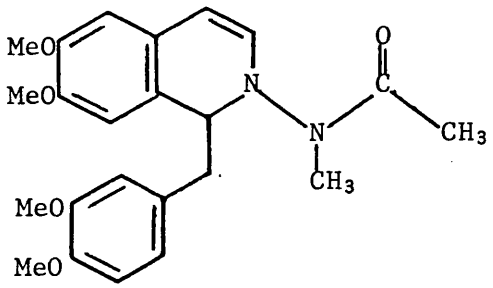


Scheme 16

likely that the mesitylenesulphonic acid salt of the ylide [(41), X = mesitylenesulphonate] had been isolated. The complexity of the spectrum made identification difficult and instead, the acetylation product was characterised as the iodide salt [(41), X = I], which was obtained as a highly crystalline solid in 20% yield, after

treating an alcoholic solution of the above product with aqueous hydriodic acid. Interestingly, a subsequent attempt to form the iodide salt [(41), X = I] did not result in the crystallisation from solution of this compound, but instead, concentration of the solution resulted in the isolation of the acetate salt [(41), X = OAc].

Methylation of the *N*-acetamidopapaverinium species (41) was achieved by warming with methyliodide in acetone to give [(33), X = I] by direct crystallisation in 42% overall from papaverine. The use of neat methyliodide, although usually successful, occasionally led to the formation of intractable tars. It was anticipated that reduction of the methiodide [(33), X = I] to the tetrahydroisoquinoline would occur readily. Thus in keeping with standard procedure for the reduction of isoquinolinium salts,[49] the methiodide [(33), X = I] was treated with sodium borohydride in aqueous ethanol. To our surprise, no tetrahydroisoquinoline was formed, either at room temperature or after prolonged boiling. Instead, a 90% yield was obtained of what appeared, on the basis of u.v. and mass spectral data, to be the 1,2-dihydroisoquinoline (42).



(42)

Confirmation of the structure was initially inhibited by the complexity of the ^{1}H n.m.r. spectrum which, instead of exhibiting two methyl group resonances, possessed four singlets at δ 1.93, 2.15, 2.78 and 3.25. The two doublets expected for the H-3 and H-4 protons were not discernible and the multiplicity of the H-1 methine

proton was greater than the expected triplet (see Figure 1). However, the spectrum was found to be temperature dependent and heating the sample to 90° C resulted in the gradual coalescence of the two sets of signals to give a simpler, but considerably broadened spectrum (Figure 2). At 130° C the spectrum was better resolved and the structural features of the 1,2-dihydroisoquinoline could clearly be deduced (Figure 3).

The $N\text{-}CH_3$ and $-COCH_3$ resonances then each appeared as singlets, the methine proton was present as a triplet and the alkenic hydrogen H-3 could be observed as a doublet (J = 8 Hz), at δ 6.13 with the coupled H-4 signal appearing as a still unresolved hump at δ 5.75. This resonance was resolved to a doublet (J = 8 Hz) at 150° C. Further evidence for the structure was obtained by reducing the methiodide (33) with d^4-sodium borohydride, which led to the disappearance from the ^1H n.m.r. spectrum of the H-1 signal and the collapse of the methylene resonance to a singlet (Figure 4). Heating a sample to >100° C with deuterium chloride in d^6-DMSO/D_2O resulted in exchange of the H-4 hydrogen, thereby demonstrating the enamine character, albeit reduced, of the system. An attempt to determine the reactivity of the enamine system at room temperature through a similar experiment merely resulted in precipitation of the compound from solution.

The temperature dependence of the spectrum may be a result of a number of factors. Analysis of models of the structure leads to the conclusion that restricted rotation about both the benzylic and N-N linkages is likely as a result of the bulkiness of the dimethoxybenzyl and *N'*-methylacetamido groups and their consequent steric interaction. To this may be added the possibility of slow inversion of the ring nitrogen atom and the existence of an intrinsic barrier to rotation within the N-N bond itself. Slow inversion[50] and energy barriers to rotation[51] within hydrazines are well known phenomena although, unless both nitrogen atoms are contained in a ring, thereby eliminating the possibility of rotation, it is often impossible to differentiate between the two effects.[51,52] However, calculations have shown that the inversion process in hydrazines requires more energy than inversion of the corresponding amine. For example,

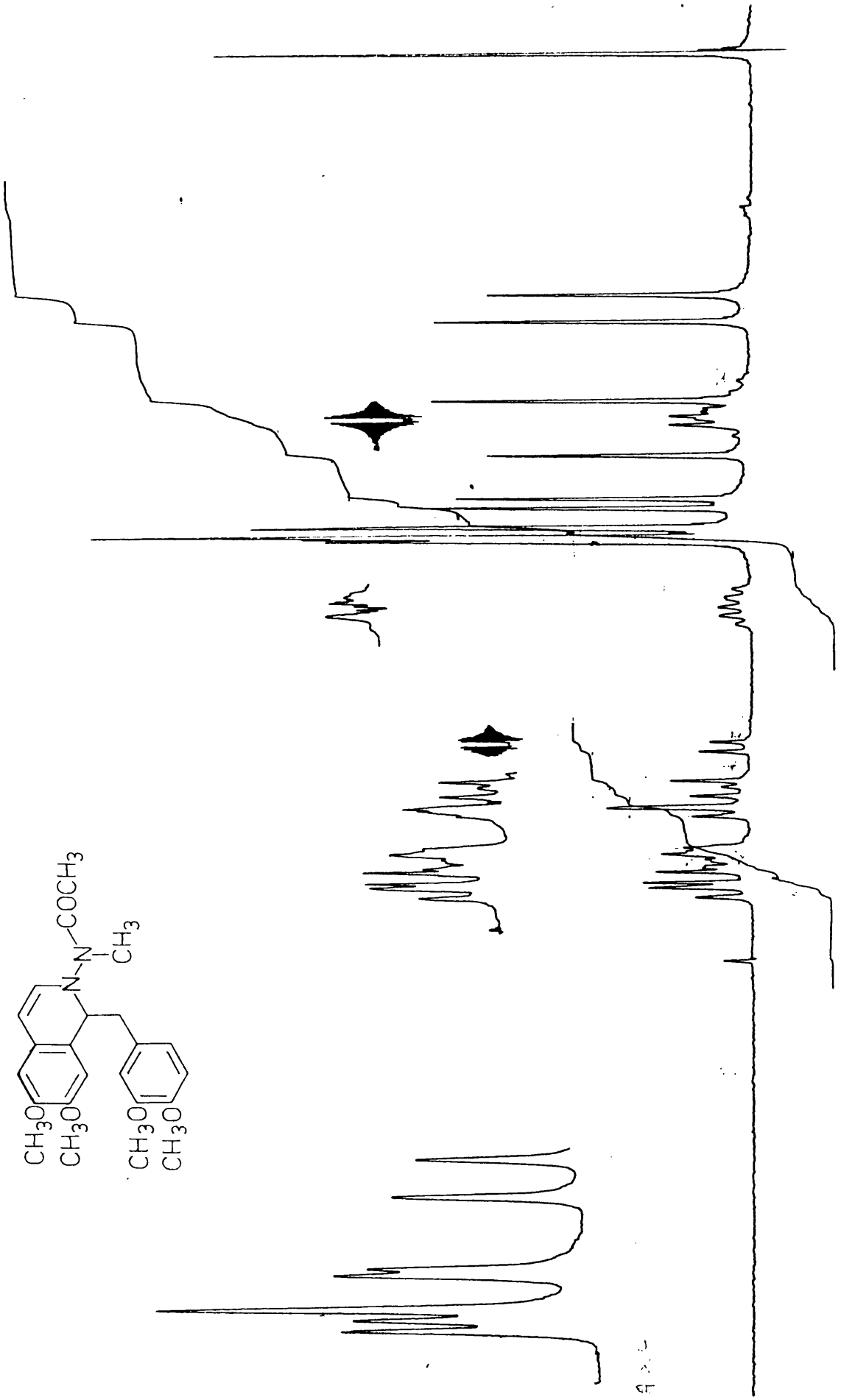


Figure 1

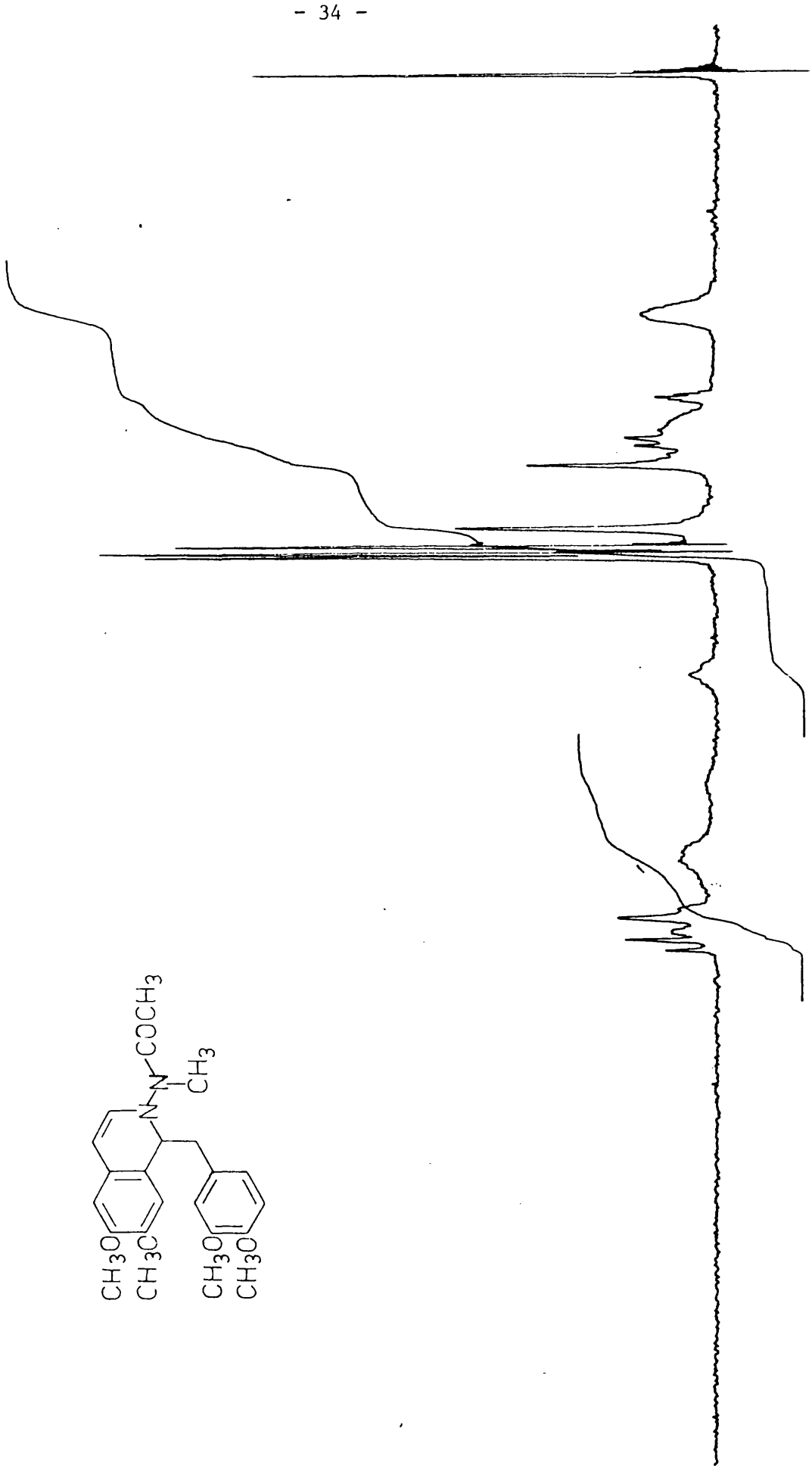


Figure 2

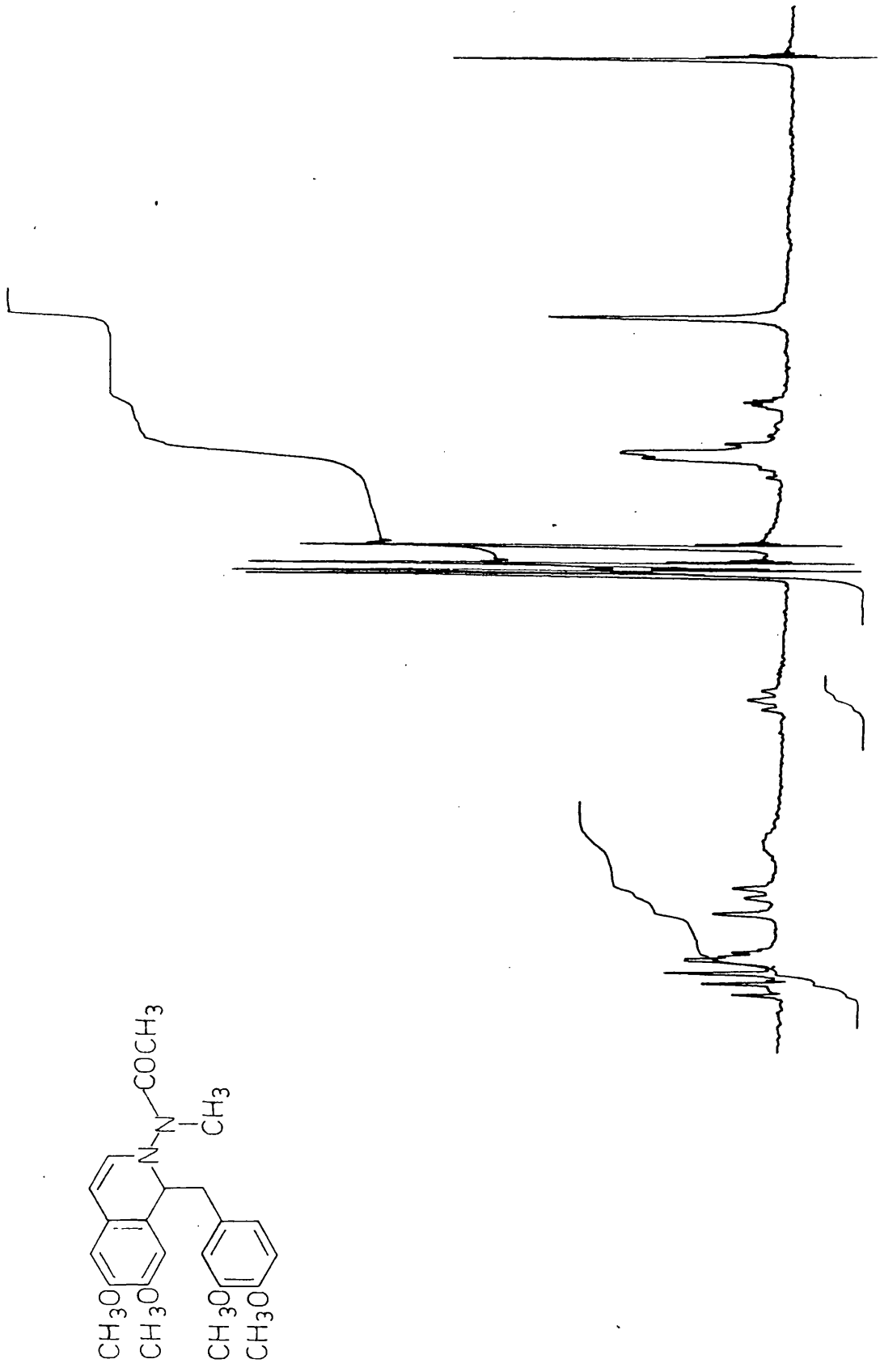


Figure 3

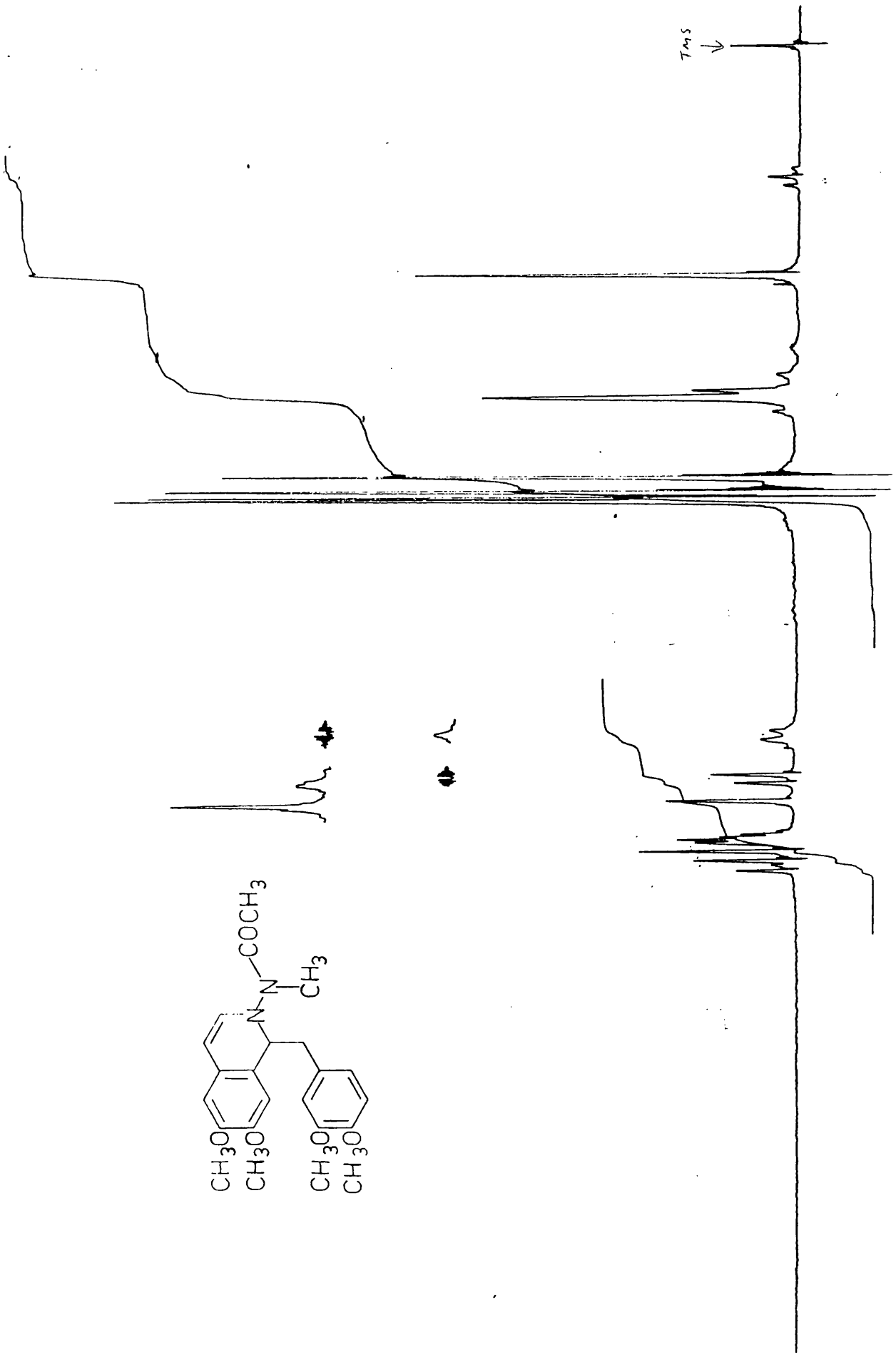
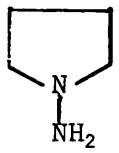
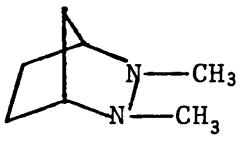


Figure 4

N-aminopyrrolidine (43) has been variously calculated to possess a barrier to inversion of 22.3 kcal/mol,[50a] or 30 kcal/mol.[50b] High values have also been obtained experimentally and the cyclic hydrazine (44), which exhibits two ^{1}H n.m.r. signals for the methyl groups at low temperatures, has a measured enthalpy of activation of 14.5 kcal/mol.[51b] A value of 16.2 kcal/mol at a coalescence temperature of 50° C has been reported for the picrylhydrazine (45).[50a] The reason



(43)



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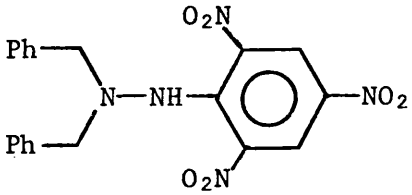


(45)

for the high barrier to inversion is not totally clear, although several partly satisfactory explanations have been offered, but it has been demonstrated to be part of a general phenomenon whereby the replacement of an amine hydrogen with an electronegative atom or group results in a slower rate of inversion. It has also been found that inversion of the nitrogens in cyclic hydrazines is slower than is the case with acylic hydrazines.

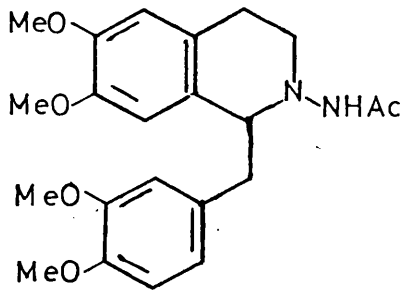
Rotational "stiffness" is more understandable and is thought to be partly due to the energy required to overcome repulsion between the non bonded nitrogen lone pairs when the molecule is in the eclipsed conformation.[53,54] The steric effect of the substituents on the nitrogen must also be taken into account. Rotational energy barriers as high as 24 kcal/mol have been recorded.[51b]

An alternative cause of the temperature dependency of the ^{1}H n.m.r. spectrum of the 1,2-dihydroisoquinoline (42) may be the existence of an *E* and *Z* isomerism about the C-N bond of the amide function. Such isomerism is, of course, well known with amides[55] and, for example, *N*,*N*-dimethylformamide possesses a rotational barrier (ΔG^*) of approximately 21 kcal/mol at a coalescence temperature (T_c) of 130° C. Similar cases of *E* and *Z* isomerism have been obtained with

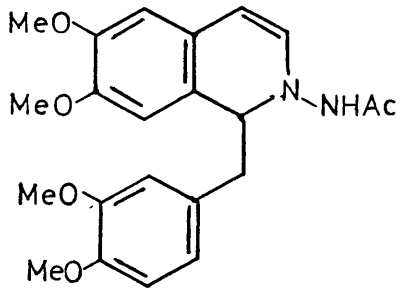
N-acylhydrazines. For instance, the multiplicity of the ^{1}H n.m.r. signals due to the methylene protons in 2-acetyl-1,1-dibenzylhydrazine is a function of temperature with coalescence of the resonances of the *E* and *Z* isomers finally taking place at 120° C.[51a]

The fact that a 1,2-dihydroisoquinoline (42) rather than a tetrahydroisoquinoline (34) was formed as the product of the reduction of the isoquinolinium methiodide [(33), X = I] requires some comment, particularly as it was found that by stirring the corresponding hydriodide salt [(41), X = I] with sodium borohydride in ethanol at room temperature, *N*-acetamidotetrahydropapaverine (46) was formed in 57% yield. The unusual stability towards acids shown by the 1,2-dihydroisoquinoline (42) also requires an explanation. On first examination it seems feasible that the steric effect of the *N'*-methyl group could be a reason for the difference in reactivity between the methiodide [(33), X = I] and the hydriodide [(41), X = I], but in view of the magnitude of the difference, this argument is not a particularly strong one.

The other important difference between the two compounds is that the *N*-acetamido-1,2-dihydroisoquinoline (47), presumed to be an intermediate in the reduction process, is capable of losing a proton in basic media, whereas the *N'*-methylacetamido homologue (42) is not. It

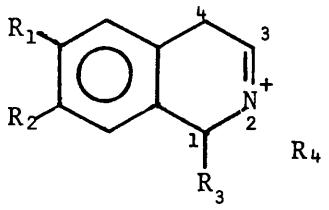


(46)



(47)

is generally accepted that further reduction of a 1,2-dihydroisoquinoline proceeds *via* protonation at the 4-position to give an iminium species (48),



(48)

which is subsequently reduced by nucleophilic attack of the reducing agent at the 3-position.[49] The protonation step requires the lone pair on the nitrogen to overlap with the orbitals of the double bond which, in turn, requires the molecule to adopt a planar configuration essentially the same as the transition state for the inversion process. If, as a result of factors already discussed, such as the electronegativity, further enhanced by the acyl substituent, of the exocyclic amino function, the inversion process is retarded, then the rate determining protonation step will not take place, or at best, will take place extremely slowly.

An alternative, but related, explanation is that the net electron withdrawing effect of the *N*-methylacetamido unit simply reduces the basicity of the ring nitrogen to such an extent that it cannot be protonated. This would explain why the 1,2-dihydroisoquinoline (42) was essentially insoluble in and inert towards acids.

In both cases the loss of a proton from the *N*-acetamido-1,2-dihydroisoquinoline (47) would render the N-substituent much less electronegative, thereby cancelling out the above effects and enabling protonation and subsequent reduction to the tetrahydroisoquinoline (46) to occur.

The arguments advanced above are complicated by the observation that the methylsulphate salt [(33), X = $CH_3OSO_3^-$] could be reduced by sodium borohydride to the tetrahydropapaverine (34) in reasonable yield. However, this reaction was found to be poorly reproducible; some attempts resulting in exclusive formation of the 1,2-dihydro-isoquinoline (42).

Having isolated and identified the 1,2-dihydroisoquinoline (42), attempts were then made to reduce it further. Prolonged boiling with sodium borohydride in ethanol was unsuccessful, as was a similar experiment conducted in boiling *n*-butanol. A final attempt to effect reduction with a boron hydride reagent was made by treating the dihydro

compound (42) with sodium cyanoborohydride in 2 M hydrochloric acid at room temperature, but again no reduction was observed. The addition of ethanol to the mixture to improve the solubility of the starting material resulted in slow formation of a number of products but none of these corresponded to the desired tetrahydropapaverine (34). Our attention was then turned to the possibility of using catalytic hydrogenation, but an initial attempt at room temperature and 30 p.s.i. pressure in ethanol solution over palladium on charcoal catalyst was also unsuccessful. Increasing the pressure of hydrogen to 200 p.s.i. gave a similar result. Hydrogenation over palladium on charcoal in glacial acetic acid solution did result in consumption of starting material, but because of the multiplicity of products, the method was considered to be unsatisfactory. Finally, successful reduction was achieved using Adams' catalyst in ethylacetate solution. Thus hydrogenation at a pressure of 250 p.s.i. for forty-eight hours resulted in clean conversion to the tetrahydropapaverine (34) in 85% yield.

2.2 An alternative route

While attempts were being made to identify and further reduce the 1,2-dihydroisoquinoline, an alternative route to *N*-[*N*'-methylacetamido]-1,2,3,4-tetrahydropapaverine (34) was developed (Scheme 17).

The first stage in this alternative process was the reduction of *N*-aminopapaverinium mesitylenesulphonate (39) with sodium borohydride in ethanol solution to give *N*-amino-1,2,3,4-tetrahydropapaverine (49) in a yield of 72% overall from papaverine (32). The spectral data for this compound were consistent with the proposed structure, although initially it was not possible to pick out, in the ^{1}H n.m.r. spectrum, the *ortho*- coupling usually associated with the veratryl ring (Figure 5). Moreover, the aliphatic resonances appeared as a complex multiplet at δ 2.5-3.6 and could not be assigned with any certainty. In an attempt to clarify the spectrum, shift reagent studies were undertaken using the reagent $Pr(fod)_3$ but no resolution of the aliphatic resonances was observed within the concentration range 0-0.29 M $Pr(fod)_3$. However, at a concentration of 0.14 M $Pr(fod)_3$ the splitting typically associated with a veratryl system became apparent (see Figure 6). The signal due

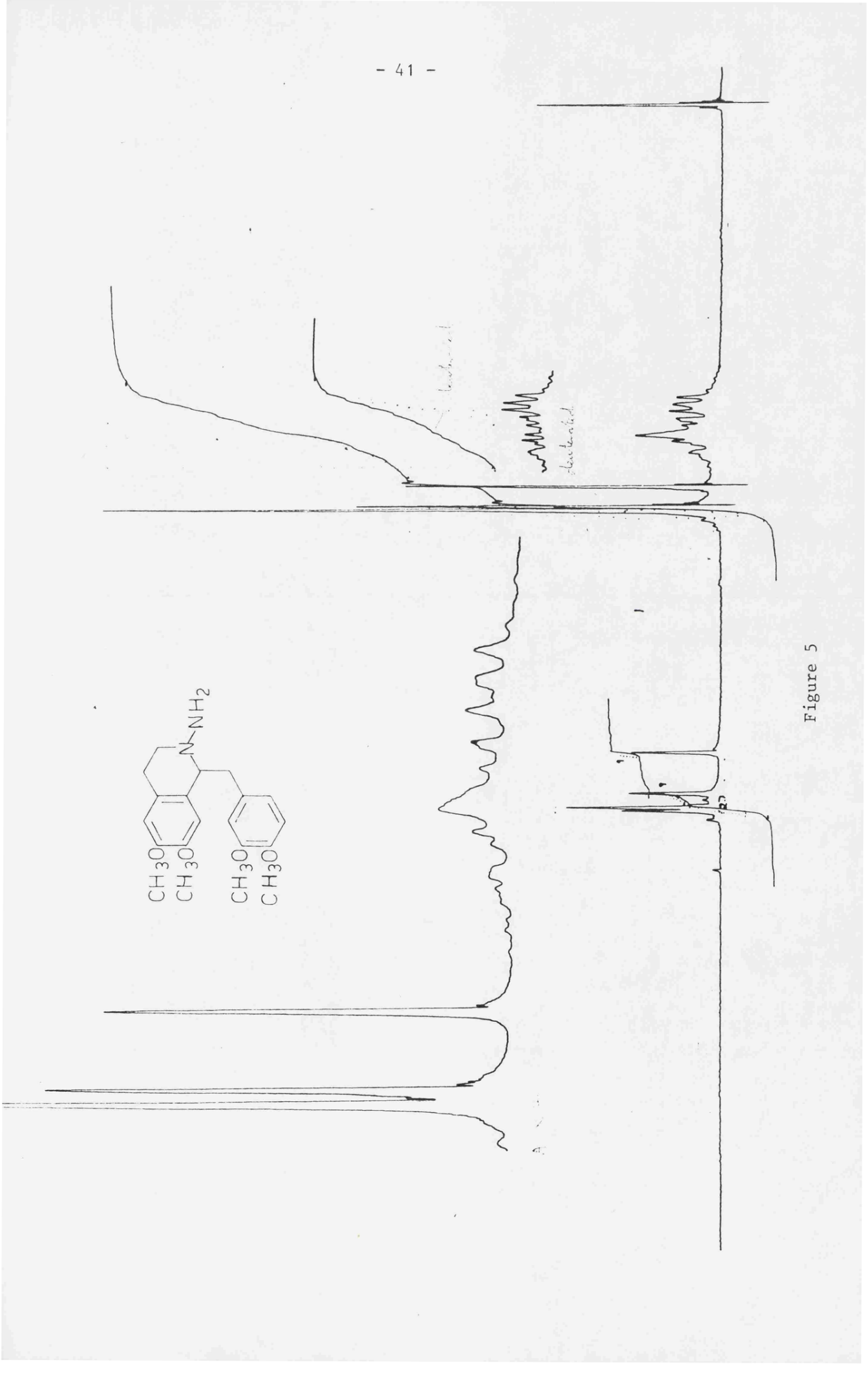


Figure 5

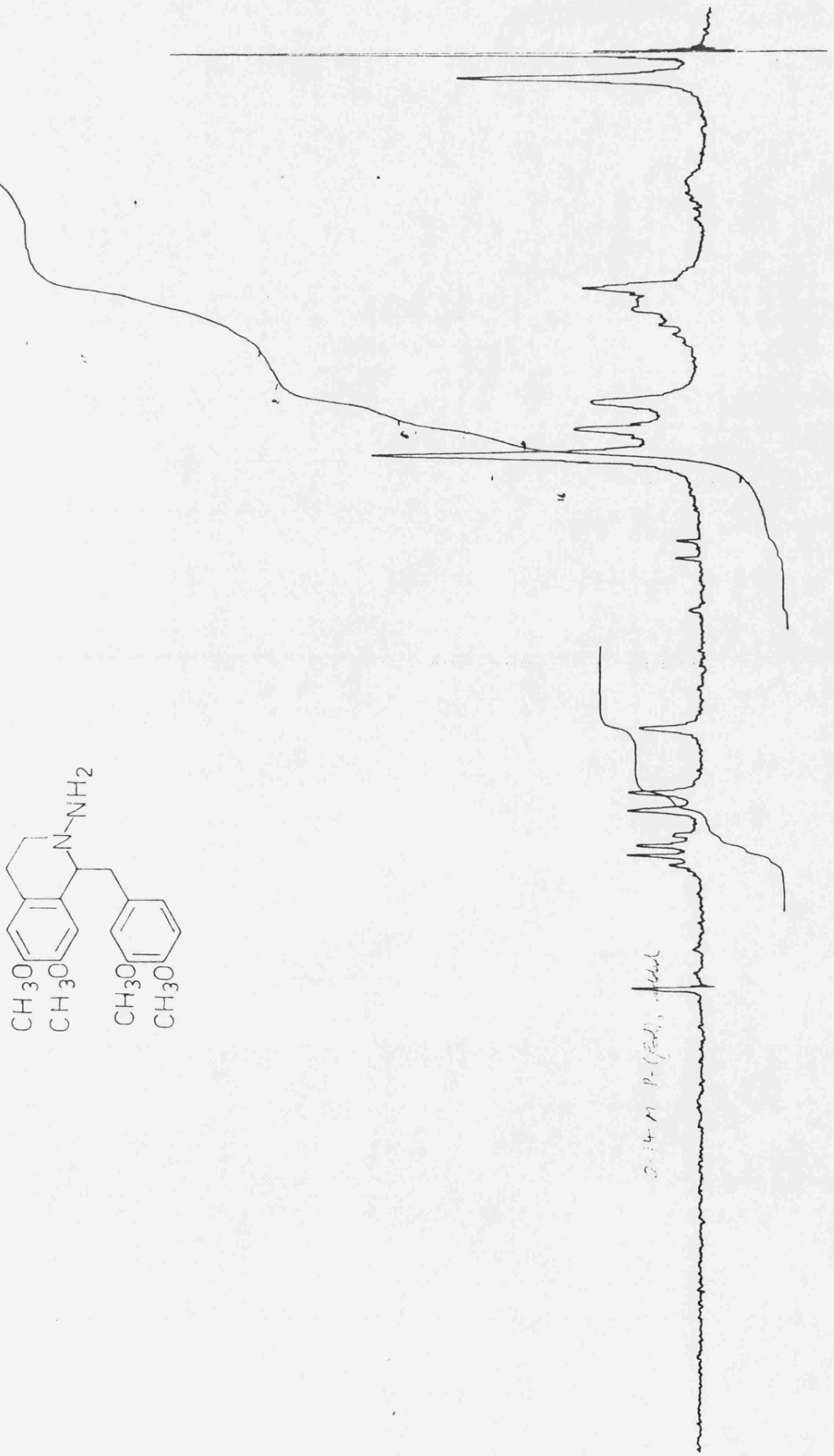
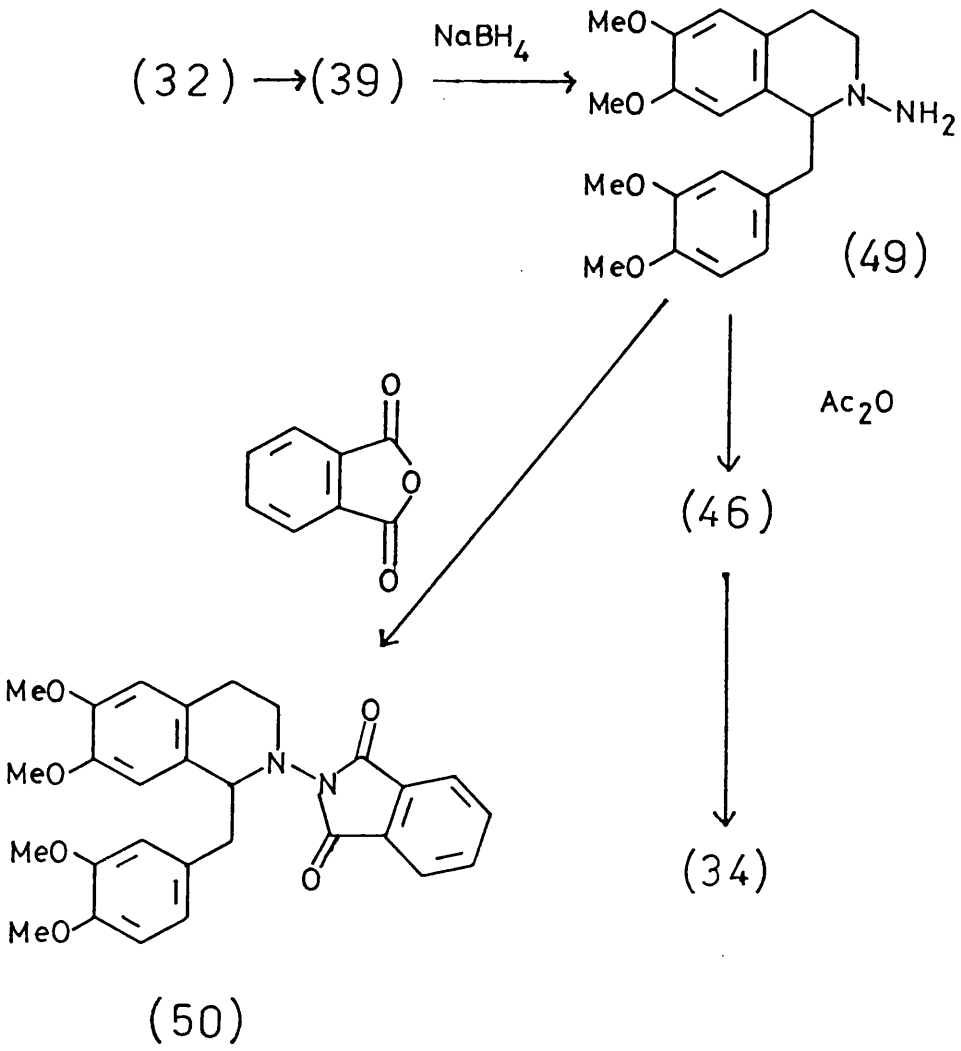


Figure 6



Scheme 17

to H-5' then appeared as a sharp doublet (J = 8 Hz) at δ 6.15 with H-6', a broadened doublet (J = 8 Hz) at δ 6.06 p.p.m. The change in the spectrum was presumably a result of the shift reagent interacting with the methoxyl groups.

The next stage of the synthesis, namely the formation of *N*-acetamido-1,2,3,4-tetrahydropapaverine, was accomplished by treatment of an ethanolic solution of the amine (49) with acetic anhydride. After work-up and recrystallisation the amide (46) was obtained as colourless needles in a yield of 76%.

The ^{1}H n.m.r. spectrum of this compound was noteworthy in that it exhibited two sets of signals for each of the N-H and CH_3-CO resonances at room temperature, probably as a result of *E* and *Z* isomerism about the C-N bond of the amide function. Heating to 150° C resulted in complete coalescence of the signals.

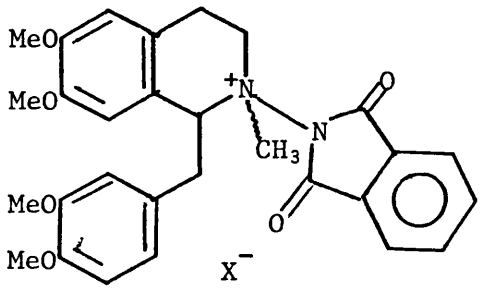
A method for the *N'*-methylation of the amide was then developed. An initial attempt using sodium hydride in tetrahydrofuran (THF) solution, followed by the quenching of the resulting N-anion with methyliodide, was only partly successful. Although a yield of 42% was obtained, the poor reproducibility of this procedure, partly a result of the limited solubility of the starting material in THF, rendered it unacceptable.

A potentially much simpler means of *N*-alkylating amides has been reported by Ando[57] who uses alumina supported potassium fluoride as the base. The supported base was thus prepared according to Ando's method by mixing potassium fluoride and alumina in water and then evaporating to dryness at 50-60° C under reduced pressure. The resulting powder was then used to treat a solution of the amide (46) and methyliodide in acetonitrile. After stirring overnight at room temperature t.l.c. analysis of the reaction mixture showed only a trace of the desired product (34), although most of the starting material had been consumed.

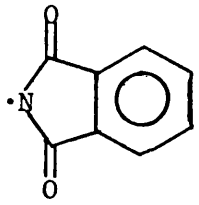
Successful *N'*-methylation was eventually achieved by forming the amide anion through reaction with sodium hydride in a mixture of dimethylformamide and dichloromethane, and then quenching with methyliodide as before. In this way a 90% yield of the *N'*-methylamide (34) was obtained with no starting material remaining.

2.3 The reactions of *N*-amido-1,2,3,4-tetrahydropapaverines with alkylating agents

Photochemical homolytic cleavage of the N-N bond of the hypothetical phthalimidomethiodide derivative (51) would give rise to the phthalimido radical (52) which, on account of the opportunities for



(51)



(52)

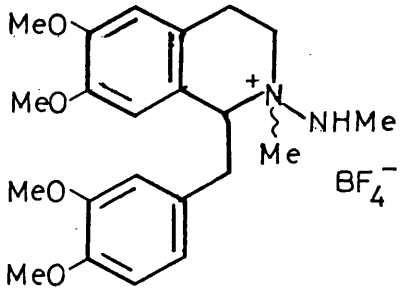
delocalisation of the odd electron, might be expected to enjoy considerable stability. With this in mind, *N*-phthalimido-1,2,3,4-tetrahydropapaverine (50) was prepared by reaction of the amino-tetrahydroisoquinoline (49) with phthalic anhydride in toluene under Dean-Stark conditions. Work-up and chromatography afforded the required compound in 62% yield. This compound, along with its *N'*-methylacetamido and acetamido analogues was then subjected to various alkylating conditions.

An acetone solution of the phthalimide (50) and excess methyl-iodide was therefore heated at reflux for 16 hours. No precipitation of a methiodide product was observed using this method and evaporation of the solvent merely resulted in the recovery of starting material. A similar result was obtained when acetonitrile was used as the solvent. The use of dimethylsulphate in acetonitrile likewise failed to effect methylation, as did heating in neat dimethylsulphate.

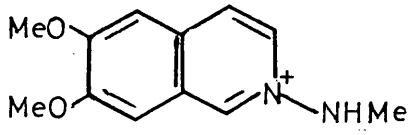
On the basis of these experiments, it appears that the phthalimido group may either be too bulky, in which case the approach of the methylating agent towards the tertiary nitrogen centre may be sterically hindered or alternatively, the electron withdrawing effect of the group

may render the ring nitrogen insufficiently basic for quaternisation to occur.

Such effects should be less noticeable with the *N'*-methylacetamido analogue (34), although the ^{1}H n.m.r. spectrum of this compound did show temperature dependence, thereby indicating the existence of barriers to rotation and/or inversion. However, the reaction of the methylamide (34) with methyliodide in acetone at reflux did not give rise to alkylation, neither did the use of dimethylsulphate as the alkylating agent. Finally, methylation was attempted using Meerwein's reagent, trimethyloxonium tetrafluoroborate. Stirring the substrate at room temperature with 1.2 equivalents of the alkylating agent eventually resulted in the disappearance of most of the starting material but removal of the solvent resulted only in formation of a brown tar, the spectroscopic analysis of which was inconclusive. Treatment of the tar with ethanol caused the formation of a crystalline solid which was tentatively assigned the structure (53). Evidence for this structure was obtained from the ^{1}H n.m.r. spectrum, although the broadness of the spectrum precluded complete characterisation, and the i.r. spectrum which did not show a peak due to a carbonyl function. In addition, the base peak in the mass spectrum, occurring at m/e 219 is possibly due to the fragment (54) which could be



(53)



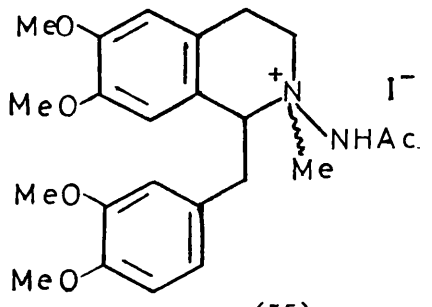
(54)

envisaged as arising through elimination of the methyl group from the parent structure followed by cleavage of the benzylic moiety and aromatisation.

If the proposed structure (53) is correct, then its formation has probably taken place *via* solvolysis of the *N*-methyl salt [(31), X = BF_4]. Relief of steric compression would be a considerable driving force in favour of solvolysis.

In view of our inability to synthesise and isolate the target methiodide [(31), X = I], the reactivity of the less sterically hindered acetamidotetrahydroisoquinoline (46) towards methylating agents was investigated.

The use of neat methyliodide at reflux followed by removal of the excess reagent gave rise to a tar from which none of the desired quaternary salt (55) could be isolated. When acetone was used as a co-solvent, boiling overnight and subsequent evaporation of the solvents yielded a solid residue from which a small amount of the methiodide (55) was obtained by recrystallisation. Prolonged reaction times using methyliodide and acetone at reflux led to slow precipitation from solution of the required product and after 69 hours, a 74% yield of 2-acetamide-2-methyl-1,2,3,4-tetrahydropapaverinium iodide was obtained by simple filtration. The identity of the product was confirmed in the usual way from the ^1H n.m.r. spectrum, i.r. spectrum and analytical data.



(55)

2.4 The photolysis of isoquinolinium salts

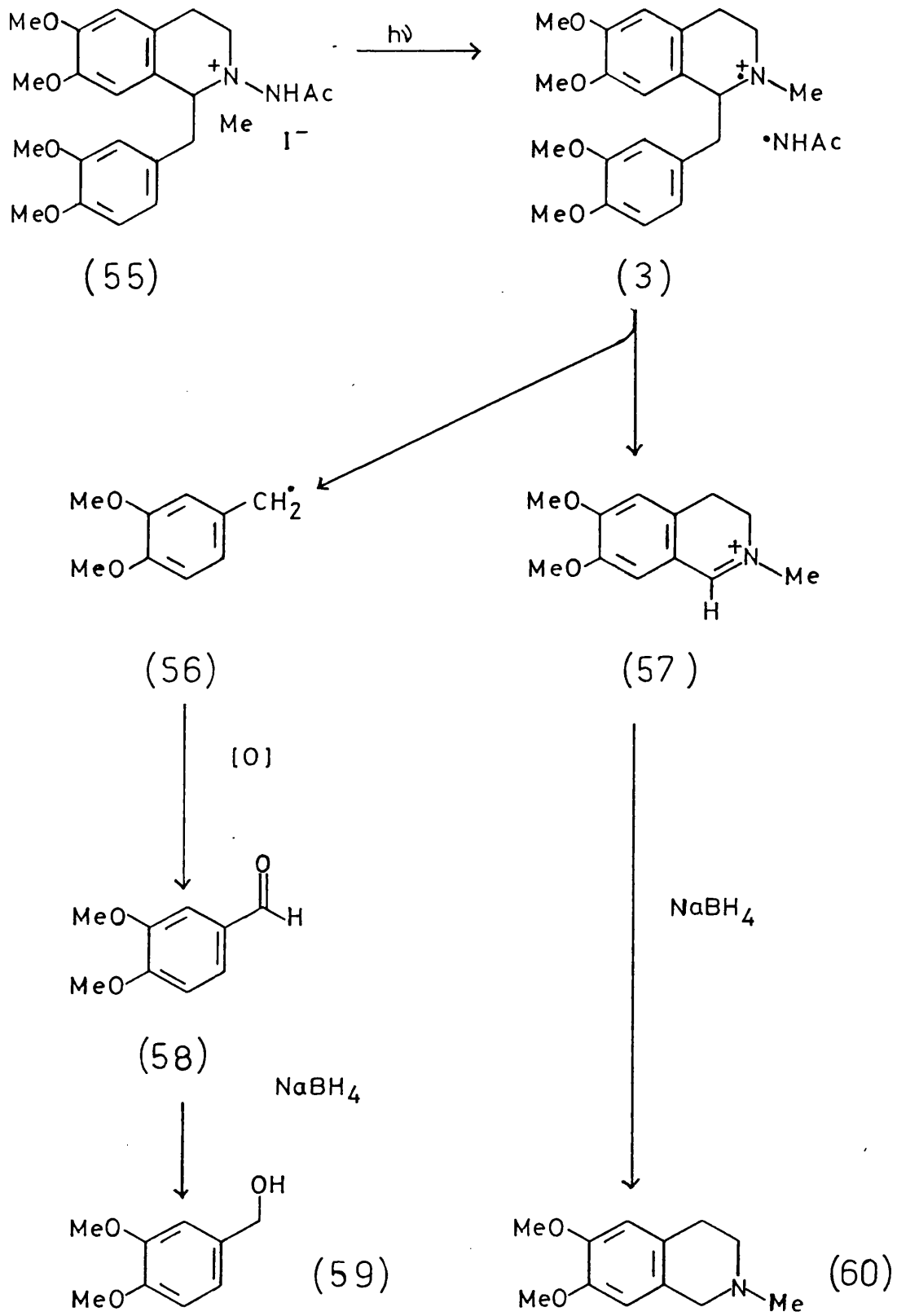
A dilute solution of the 2-acetamido-2-methylisoquinolinium salt (55) in methanol was subjected to irradiation with a 125 W medium pressure u.v. lamp. The progress of the reaction was monitored closely by withdrawing samples for u.v. analysis and t.l.c. comparison with veratraldehyde (58) and *O*-methylflavinantine (2). The appearance

of veratraldehyde (58) was observed after only 15 minutes. After 3 hours, half of the reaction mixture was evaporated down and partitioned between ethylacetate and dilute alkali. The organic phase was subjected to chromatography and a small quantity of veratraldehyde obtained. No *O*-methylflavinantine was detected.

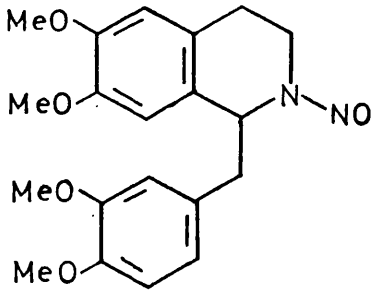
The remaining half of the reaction mixture was reduced with sodium borohydride and the crude product subjected to mass spectrometric analysis. At low voltage, peaks at m/e 207 and m/e 168 were observed, corresponding to 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (60) and veratryl alcohol (59).

It therefore appears that homolytic cleavage of the N-N bond in the salt (55) was occurring as predicted, but the resulting radical cation, rather than cyclising to *O*-methylflavinantine, underwent further fragmentation instead, to give a dimethoxybenzyl radical (56) and an isoquinolinium salt (57). Oxidation of the radical would then give veratraldehyde which could subsequently be reduced to veratryl alcohol by the action of sodium borohydride. The isoquinolinium salt could also be reduced to give the tetrahydroisoquinoline (60) (see Scheme 18).

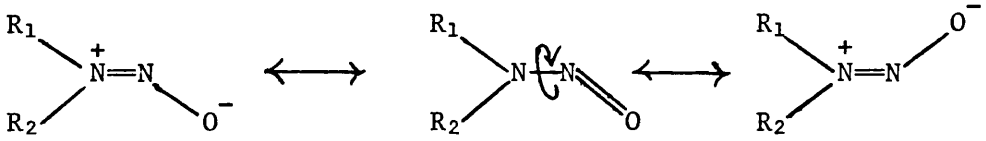
Although the intermediacy of the radical cation may be inferred from the nature of the products, and it is difficult to see how they could have arisen *via* an alternative mechanism, we felt that additional proof was required. The photolysis of nitrosamines in acid solution is known to result in aminium ion formation and in this case,[10] the nature of the intermediate has been established by flash photolysis studies (see Chapter 1). The nitrosamine (61) was therefore synthesised by treating tetrahydropapaverine hydrobromide with sodium nitrite and hydrochloric acid. Characterisation of the product was initially inhibited by the complexity of the ^{1}H n.m.r. spectrum caused by an unusually high barrier to rotation about the N-N bond. Simple nitrosamines are known to possess rotational energy barriers of *ca.* 20-25 kcal/mol as a result of the considerable double bond character of the N-N linkage [equation (20)].[58]


MeO
MeO
MeO
MeO
+N
NHAc
Me
I⁻
hν
Me
•NHAc
(55)
(3)
CH₂•
(56)
(57)
[O]
O
H
(58)
NaBH₄
NaBH₄
OH
(59)
(60)

Scheme 18



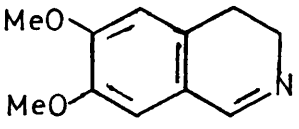
(61)



(20)

In the case of our compound, although heating did result in an improvement in resolution, probably as a result of faster rotation of the benzylic moiety, no tendency towards coalescence of the resonances attributed to the *E* and *Z* forms was observed even at 120° C.

A solution of the nitrosamine in methanol that contained hydrochloric acid was irradiated with a 125 W u.v. lamp for 13 hours, the reaction being monitored by u.v. and t.l.c. As observed in the preceding photolysis, the appearance of veratraldehyde was noted shortly after the commencement of the irradiation period. After work-up and chromatography, veratraldehyde was again isolated and was accompanied this time by 6,7-dimethoxy-3,4-dihydroisoquinoline (62),



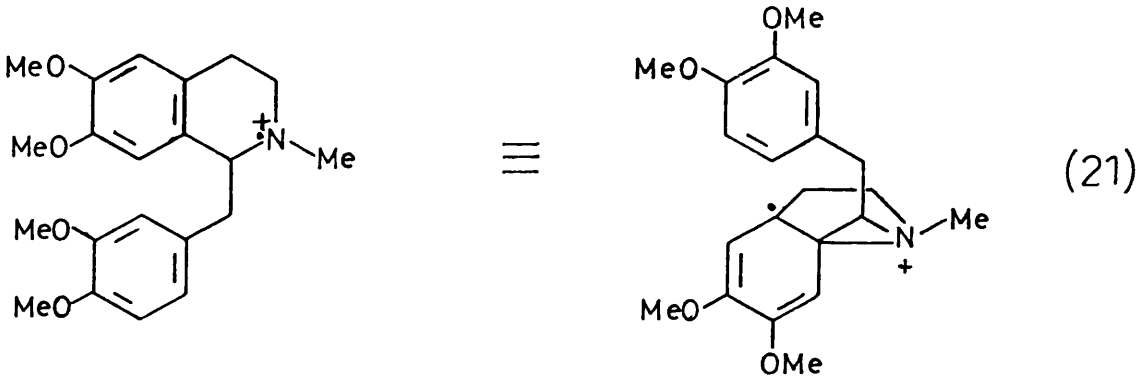
(62)

the two products being characterised in the usual way.

2.5 Conclusion - a new proposal for the mechanism of the anodic cyclisation of laudanosine to *O*-methylflavinantine

It is pertinent at this point to reconsider a number of the facts concerning the anodic cyclisation of laudanosine in neutral solution at low potential. As previously mentioned, Miller[2] has reported that

formation of *O*-methylflavinantine occurs in the electrochemical cell at +0.6 V, but that yields are variable. In the majority of cases veratraldehyde and 6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolinium ion are formed in appreciable quantities. At 0.6 V it is highly likely that formation of the aminium radical ion (3) is occurring through loss of one electron from the lone pair and Miller has postulated that cyclisation takes place from this aminium ion through a mechanism involving anchimeric assistance between the radical cationic centre and the isoquinoline aromatic ring. However, the photolysis



(3) ≡ (21)

of 2-methyl-2-acetamido-1,2,3,4-tetrahydropapaverine (55) also gives rise to the aminium ion (3) and yet in this case no *O*-methylflavinantine is formed. A related photolysis involving the protonated form of the nitrosamine (61) similarly fails to result in formation of the *N*-demethyl analogue of *O*-methylflavinantine. The radical cation proposed by Miller has thus been formed in an unambiguous manner through an unrelated process and has been shown not to cyclise. Miller's theory, although plausible, must therefore be incorrect.

It has also been suggested that a further oxidation, either of the radical cation, or of an initial hypothetical cyclisation product may be required in order that formation of *O*-methylflavinantine can take place. Intuitively, this seems unlikely, since the loss of one electron from the molecule would surely result in the remaining

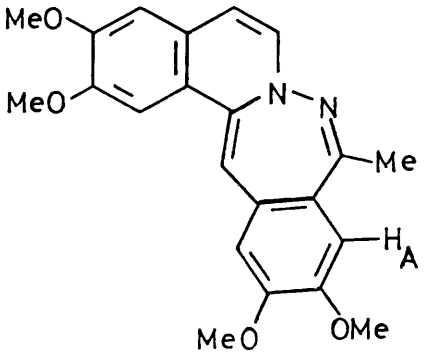
electrons being bound more tightly, thereby raising the potential required for further electron loss to take place.

Miller's observation that yields of cyclisation products are variable and are nearly always accompanied by formation of an aldehyde (58) and a 3,4-dihydroisoquinoline (57) is put into perspective by the discovery in this laboratory that the anodic cyclisation is concentration dependent and that in very dilute solution no *O*-methylflavinantine is formed at all. The aldehyde (58) and the 3,4-dihydroisoquinoline are the sole isolable products in this case. The implication here is that an intermolecular process is involved in the cyclisation. Such a process could take the form of an electron transfer to the electron deficient nitrogen from the dimethoxylated aromatic ring of an adjacent molecule to give a new "π" radical cation, which could then cyclise. Although the ionisation potentials for the lone pair of the nitrogen and the π-electrons of the dimethoxylated aromatic ring differ by ~0.5 V, this is a reasonable suggestion provided that the first radical cation is relatively stable and the second decomposes into product rapidly and irreversibly. A precedent for this type of process does exist and, for example, the polarographic reduction of a number of aromatic compounds in the presence of a more easily reduced "catalyst" has been reported by Lund *et al.*[60] In this work the differences between the ionisation potentials of the "catalyst" and the substrate were typically 0.3-0.55 volts.

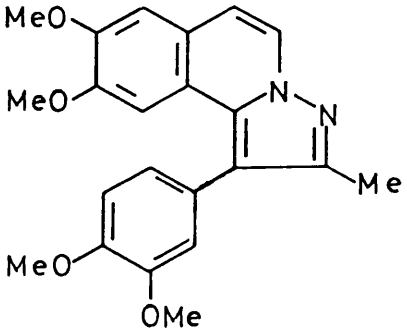
2.6 The synthesis of a pyrazolo[5,1-*a*]isoquinoline

During an attempt to prepare the 1,2-dihydroisoquinoline (42) on a large scale in order to carry out further experiments to ascertain its reactivity towards various reduction conditions, the formation of a highly fluorescent side product was observed. This hitherto unnoticed compound was subsequently isolated in *ca.* 4% yield by chromatography of the crude mixture obtained from the sodium borohydride reduction stage and was subjected to the usual spectroscopic analysis.

The mass spectrum indicated a molecular formula of $C_{22}H_{22}N_2O_4$, the i.r. spectrum did not include an absorption due to a carbonyl group and the ^1H n.m.r. spectrum, run in $CDCl_3$ (see Figure 7) did not exhibit the expected *ortho* and *meta* spin-spin couplings typical of a veratryl ring system. On the basis of this evidence the compound was initially assigned the diazepine structure (63).

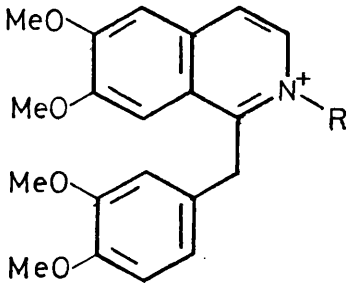


(63)



(64)

However, compounds containing a 3,4-dimethoxylated phenyl group do not always show evidence of *ortho* and *meta* splitting patterns in the ^1H n.m.r. spectrum. For example, although coupling constants of J_{ortho} = 9 Hz and J_{meta} = 2 Hz are discernible in the spectrum of papaverine methiodide [(65), R = CH_3] run in d^6-DMSO, the veratryl ring proton resonances of the related salt papaverine hydriodide [(65), R = H] in the same solvent appear as two singlets due to one and two protons at δ 7.35 and δ 6.5 p.p.m. respectively.



I^-

(65)

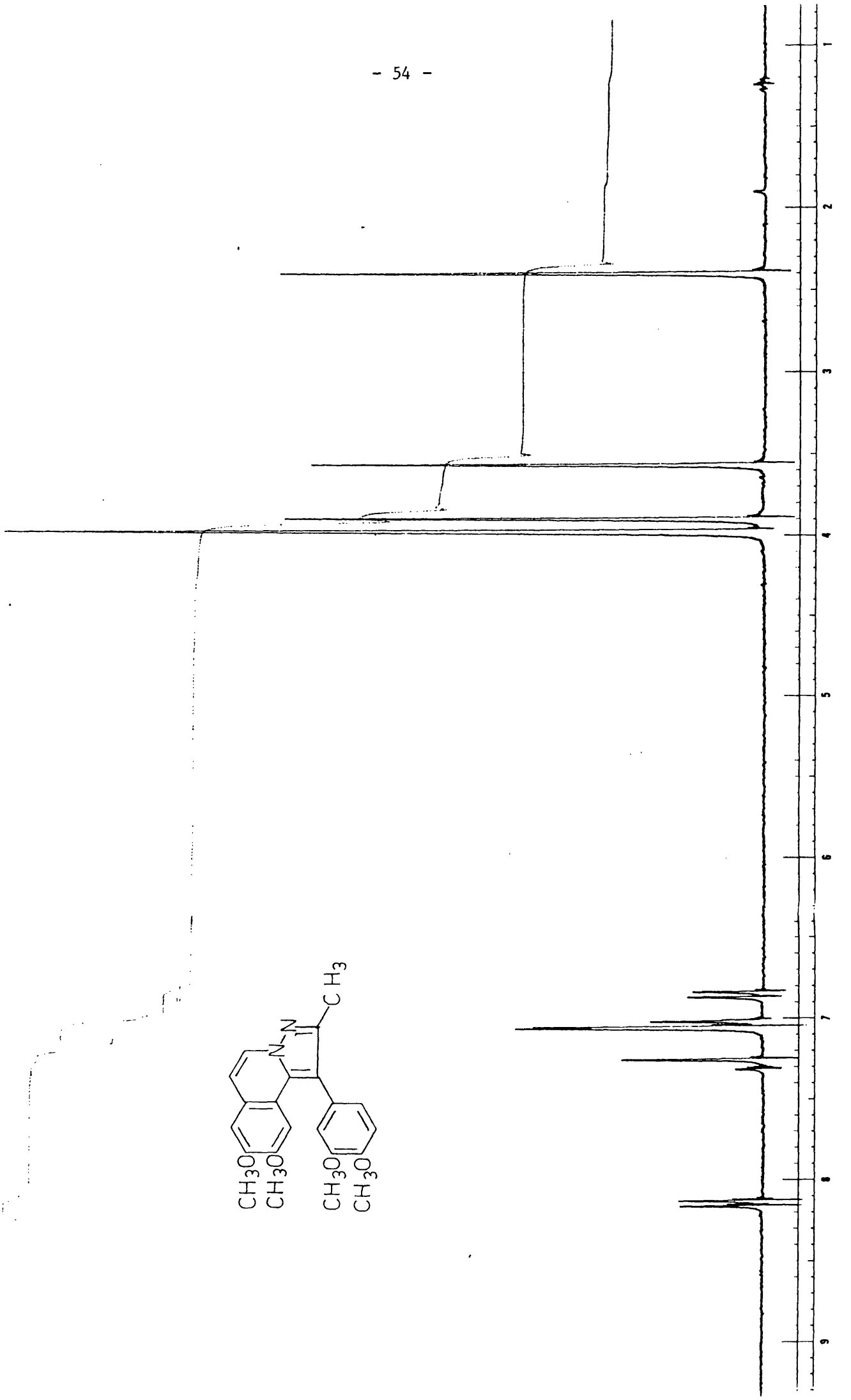
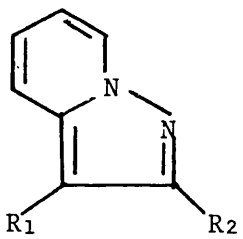


Figure 7

Clearly, more evidence was required before an alternative structure, namely that of the pyrazoloisoquinoline (64), could be ruled out. To provide such evidence, the n.O.e. spectrum was recorded, in anticipation that should the fluorescent compound possess the diazepine structure (63), then irradiation of the methyl resonance at δ 2.4 would lead to enhancement of the signal due to the aromatic proton H_A. In practice, the enhancement of two aromatic signals was observed, a fact which is not consistent with the diazepine structure (63).

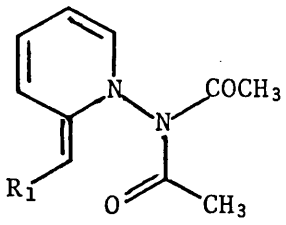
The problem was finally solved by obtaining the ^1H n.m.r. in d^6-acetone solution. This clearly showed coupling constants of magnitude J_{ortho} = 8 Hz and J_{meta} = 2 Hz, thereby proving that the fluorescent compound has the pyrazoloisoquinoline structure (64).

Several mechanisms may be postulated to account for the formation of the pyrazoloisoquinoline (64). As mentioned in Chapter 1, Potts has reported that pyrazolopyridines are formed when *N*-aminopyridinium salts are heated with acetyl chloride in pyridine, but no mechanism for this reaction was proposed.[37] In view of the low susceptibility of an amide carbonyl function to nucleophilic attack, it seems unlikely that cyclisation to the pyrazolopyridine (66) occurs through the intermediacy of the monoacylated amine.

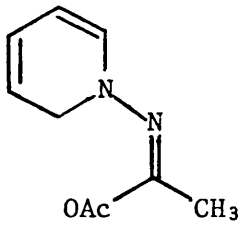


(66)

A more plausible explanation is that ring closure takes place *via* intramolecular enamine attack upon a diacetylated amino function followed by loss of acetic acid. Two possible intermediates in this process are the species (67) and (68).

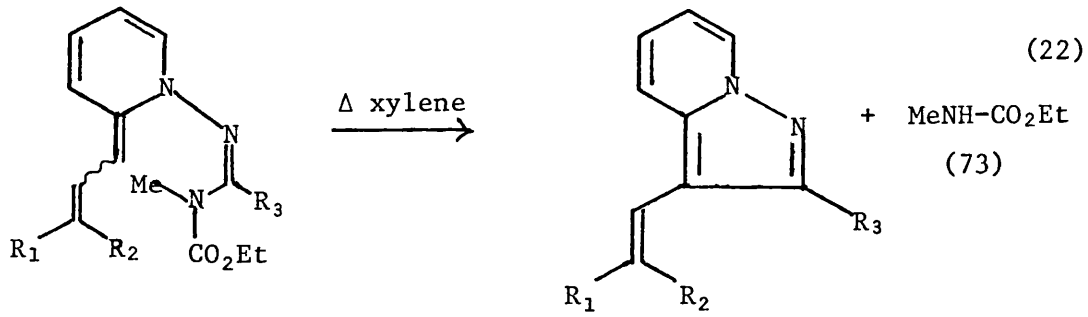


(67)



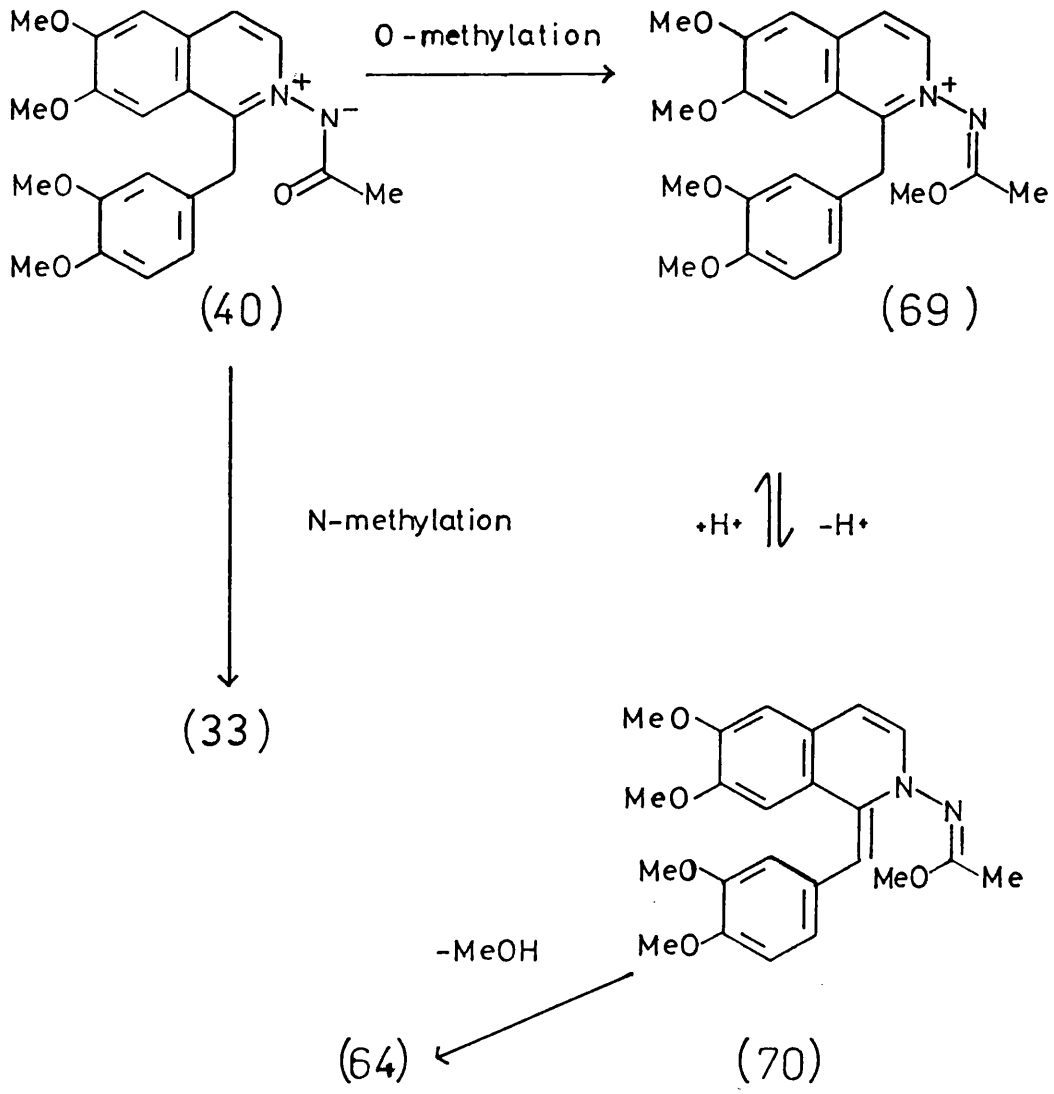
(68)

In our case, it was quickly established that the pyrazoloisoquinoline (64) did not arise through acetylation of *N*-aminopapaverinium mestiylenesulphonate (39) with acetic anhydride even when the acetylating mixture was heated to 60° C. Instead, the appearance of the fluorescent compound was observed during the methylation stage. A possible mechanism for its formation involves initial *O*-methylation of the ylid (40) followed by cycloelimination of methanol as shown in Scheme 19. An analogous cyclisation has been reported by Kakehi *et al.*,[44] who synthesised allylidenedihydropyridines (71) of the type shown in equation (22) and subjected them to thermolysis in xylene. As a result, pyrazolopyridines (72) were isolated in good yield and ethyl-*N*-methylcarbamate (73) was detected by g.l.c. as the elimination product.



(71) (72) (73) (22)

An interesting aspect of the pyrazole syntheses outlined above is that they are all samples of 5-*endo*-trig type processes which, according to Baldwin,[61] are energetically disfavoured and therefore unlikely to occur if an alternative lower energy pathway is available.



Scheme 19

This may help to account for the low yield of pyrazoloisoquinoline isolated in our synthesis, although a more probable reason is that the product distribution simply reflects the preference of methyliodide for *N*-alkylation rather than *O*-alkylation. If this theory is correct, it should be possible to increase the yield of the fluorescent compound

(64) by treating the ylide (40) with methylating agents which show a preference for *O*-alkylation.

Dimethylsulphate has been successfully used to *O*-methylate amides[62] and so a solution of the acetylated amine (40) in benzene was treated with this reagent at room temperature in the presence of a trace of triethylamine. Within a few minutes t.l.c. analysis showed the presence of some of the desired product, but prolonged stirring did not result in an appreciable increase in concentration and finally the *N*-methylated product [(33), X = $MeOSO_3$] was obtained by direct filtration in 72% yield overall from papaverine. However, by reacting the acetylated amine (40) with an excess of freshly prepared diazomethane, the yield of pyrazoloisoquinoline was increased to 10%. Moreover, no *N*-methylated product was detected and, instead, treatment of the mother liquors with aqueous hydriodic acid led to the slow formation of *N*-acetamidopapaverinium iodide [(41), X = I] in 21% yield. It is conceivable that exhaustive treatment of the reaction mixture with diazomethane would raise the yield to more acceptable levels, but such a course of action was not followed.

CHAPTER 3

E X P E R I M E N T A L

General Procedures

Unless otherwise stated, ultraviolet spectra were recorded as solutions in 98% ethanol, infra-red data refer to Nujol mulls and ^{1}H n.m.r. spectra were recorded at 100 MHz using tetramethylsilane as an internal standard. Chemical ionisation mass spectrometric analyses were carried out using isobutane as the ionising medium. Photolyses were performed with a Hanovia photochemical reactor using a 125 W medium pressure lamp with a quartz immersion well. Magnesium sulphate was used as the drying agent unless otherwise indicated. Dry acetonitrile and dichloromethane were obtained by distillation from phosphorus pentoxide.

Ethylacetimidate hydrochloride (36).-Hydrogen chloride gas was bubbled through a well cooled solution of dry acetonitrile (134 cm^3) in absolute ethanol (135 cm^3) and dry ether (170 cm^3) for 5 h. The solvents were then removed leaving ethylacetimidate hydrochloride as a colourless solid (269 g, 85%).

1-Ethoxy-1-oximidoethane (37).-Ethylacetimidate hydrochloride (100 g) was added with vigorous stirring to an ice cold solution of potassium carbonate (224 g in 500 cm^3 water). The mixture was well shaken for 10 min and then extracted into ether. The ether layer was separated, cooled to 5° C and a cold solution of hydroxylamine hydrochloride (60.4 g in 280 cm^3 water) was added. After vigorous mixing, the ether layer was removed, dried and evaporated to give the title compound as a colourless oil (585 g, 70%) that crystallised in long needles when chilled. (60 MHz) ^1H n.m.r. $\delta(CDCl_3)$: 8.55 (1H, s, N-O<u>H</u>), 4.00 [2H, q (J = 7 Hz), $-CH_2-$], 2.00 (3H, s, CH_3), 1.3 [3H, t (J = 7 Hz), $CH_2-\underline{CH_3}$]; ν_{max} (cm^{-1}): 3340, 1660, 1375, 1295.

Mesitylenesulphonylchloride.-Chlorosulphonic acid (167 cm^3) was cooled to -15° C on a salt/ice bath and mesitylene (86 cm^3, 100 g) was added dropwise at such a rate that the temperature did not rise above 5° C. When addition was complete, the mixture was stirred for a further 30 min before pouring onto ice. The crude solid acid chloride was eventually filtered off and dissolved in ether (300 cm^3). The ether solution was washed successively with saturated sodium bicarbonate solution (150 cm^3) and water (150 cm^3) before drying and evaporating at room temperature. The title compound was obtained as a slightly off-white crystalline solid (160 g, 88%). M.p. (ether/petrol) = 56-58° C (lit.,[63] 57° C).

Ethyl O-(mesitylenesulphonyl)-acetohydroxamate (38).-A solution of 1-ethoxy-1-oximidoethane (58.5 g) in dimethylformamide (200 cm^3) and triethylamine (88 cm) was cooled to 0° C and mesitylenesulphonylchloride (124 g) added cautiously, care being taken to avoid a large

temperature rise. After stirring for 1 h, the mixture was poured onto ice and scratched vigorously to effect solidification of the oil. The resulting tan coloured precipitate was filtered and freeze dried. Yield = 100 g (61%). This product was sufficiently pure for use in the next stage of the synthesis and could be stored in the freezer without noticeable decomposition for prolonged periods. A small sample was recrystallised from petrol to give a colourless solid, m.p. 54.5-55.5° C (lit.,[47] 54-56° C); (60 MHz) ^{1}H n.m.r. $\delta(CDCl_3)$: 7.20 (2H, s, aryl protons), 4.1 [2H, q (J = 7.5 Hz), $-CH_2-$], 2.80 (6H, s, mesitylene-2 and 6-methyl protons), 2.40 (3H, s, mesitylene-4'-methyl protons), 2.16 (3H, s, CH_3), 1.27 [3H, t (J = 7.5 Hz), $-CH_2-CH_3$].

O-*Mesitylenesulphonylhydroxylamine (35)*.-Method 1.[47] Ethyl *O*-(mesitylenesulphonyl)-acetohydroxamate (33 g) was suspended in 60% perchloric acid (93 cm) and the resulting mixture stirred at room temperature for 10 min, or until all the starting material had dissolved. The solution was then poured onto ice and the resulting precipitate eventually filtered off. This crude product was dissolved in ether and washed successively with saturated sodium bicarbonate solution and water, before drying and evaporating down at room temperature to afford the title compound as a colourless solid (11.51 g, 46%).

Method 2.[48] Ethyl *O*-(mesitylenesulphonyl)-acetohydroxamate (7.6 g) was dissolved in dioxan (5 cm^3) and the solution cooled to 0° C. A solution of 62% perchloric acid (3 cm^3) was then added dropwise at such a rate as to maintain the temperature below 10° C. After stirring for 10 min the mixture was poured into ice water to precipitate the crude MSH which was filtered off and then dissolved in ether (30 cm^3). The ethereal solution was washed with water (40 cm^3), treated with anhydrous potassium carbonate (5 g) for 30 sec, filtered and then poured into cold pentane (300 cm^3). After a short while the MSH precipitated as small colourless crystals (2 g) which were filtered and briefly sucked dry at the pump.

(60 MHz) ^{1}H n.m.r. $\delta(CDCl_3)$: 6.9 (2H, s, aryl protons), 5.85 (2H, bs, NH), 2.6 (6H, s, mesitylene-2 and 6-methyl protons), 2.25 (3H, s, mesitylene-4-methyl protons).

N-Aminopapaverinium mesitylene sulphonate (39).-Papaverine (1 g) in dry dichloromethane (10 cm) was cooled in an ice bath and treated with an ice cold solution of mesitylene sulphonylhydroxylamine (0.63 g) in dichloromethane (6 cm). The pale-yellow reaction mixture was stirred under a nitrogen atmosphere at 0° C for 90 min and then poured into dry diethyl ether, whereupon the title compound separated out as a solid (1.2 g, 73.4%). Exposure of this product to the air resulted in rapid uptake of water and transformation of the solid to a gum. Prolonged exposure to the atmosphere, or trituration in ether caused the gum to resolidify as the hydrated salt, which was recrystallised from ethanol, m.p. 119-120° C. ^{1}H n.m.r. $\delta(d^6$-DMSO): 8.56 [1H, d, (J = 7 Hz), H-3], 8.18 [1H, d, (J = 7 Hz), H-4], 8.01 (2H, bs, $\underline{NH}_2$), 7.79 (1H, s, H-5), 7.71 (1H, s, H-8), 7.15 (1H, s, H-2'), 6.9-6.6 (4H, m, H-5', H-6' and mesitylene ring protons), 5.06 (2H, bs, $\underline{CH}_2$), 4.00, 4.05 (6H, 2 x s, 2 x $O\underline{CH}_3$), 3.75, 3.68 (6H, 2 x s, 2 x $O\underline{CH}_3$), 3.5 (2H, bs, $\underline{H}_2O$), 2.55 (6H, s, 2 x $C\underline{H}_3$, 2-, 6-mesitylene methyl protons), 2.16 (3H, s, $C\underline{H}_3$, 4-mesitylene methyl protons): m/e 354 (M^+, very low intensity), 339 (base peak - due to loss of NH_2), 324, 308; ν_{max} (cm^{-1}): 3460, 3310, 1604 [Found: C, 60.5; H, 6.2; N, 5.05. $C_{29}H_{34}N_2O_7S$, H_2O requires: C, 60.8; H, 6.3; C, 4.9%]; λ_{max} (nm): 228, 256, 280(sh), 317, 349(sh).

6,7-Dimethoxy-1-(3',4'-dimethoxybenzyl)-2-(N-methylacetamido)-isoquinolinium iodide [(33), X = I].-*N*-Aminopapaverium mesitylene sulphonate (4 g) in 98% aqueous ethanol (15 cm^3) was cooled to 0° C and acetic anhydride (5 cm) was added. After stirring for 20 min, water (25 cm^3) was introduced and the mixture made basic with potassium carbonate, prior to extraction with dichloromethane (2 x 15 cm^3). The combined extracts were dried over magnesium sulphate and the solvent removed under reduced pressure at 20° C to give an oil which was taken up in acetone (25 cm^3) and treated with methyl-iodide (9 cm^3). After heating at reflux for 10 min, a solid separated

out. This was collected and washed with a small volume of cold acetone (2 g, 42%). The product is unstable and decomposes on heating in a variety of solvents, but as prepared it is quite pure, m.p. 194.5-196° C. ^{1}H n.m.r. δ(d^6-DMSO):* 8.82 [1H, bd, (J = 7 Hz), H-3], 8.43 [1H, bd, (J = 7 Hz), H-4], 7.89 (1H, bs, H-5, H-8), 7.05 (1H, bs, H-2'), 6.88 [1H, bd, (J = 8 Hz), H-2'], 6.72 (2H, m, H-3', H-6'), 4.94 (2H, bs, $C\underline{H}_2$), 4.11, 3.96 (6H, 2 x s, 2 x $OC\underline{H}_3$), 3.71 (6H, s, 2 x $OC\underline{H}_3$), 3.66 (3H, s, $NC\underline{H}_3$), 2.39 (3H, s, $C\underline{H}_3CO$); m/e 410 (100%, M-HI), 395, 378, 367, 338, 324; ν_{max} (cm^{-1}): 1700; λ_{max} (nm): 222, 260, 327 [Found: C, 51.3; H, 5.4; N, 5.7; I, 23.3. $C_{23}H_{27}N_2O_5I$ requires: C, 51.3; H, 5.1; N, 5.2; I, 23.6%].

6,7-Dimethoxy-1-(3',4'-dimethoxybenzyl)-2-(N-methylacetamido)-isoquinolinium methylsulphate [(33), X = CH_3OSO_3].-Papaverine (2.8 g) was aminated and acetylated as described above. The resulting gum was dissolved in dry benzene (30 cm^3) and dimethylsulphate (0.65 cm^3) was added. Triethylamine (0.4 cm^3) was introduced and the solution stirred at room temperature overnight. The resulting precipitate was filtered off, washed well with benzene and then air dried to give the title compound as a canary-yellow solid (3.1 g, 72%), m.p., 189° C (dec). ^{1}H n.m.r. δ(d^6-DMSO): 8.75 [1H, d (J = 7 Hz), H-3], 8.4 [1H, d (J = 7 Hz), H-4], 7.86 and 7.9 (2H, 2 x s, H-5 and H-8), 7.02 (1H, bs, H-2'), 6.88 [1H, d (J = 8 Hz), H-5'], 6.72 [1H, d (J = 8 Hz), H-6'], 6.92 (2H, bs, $-CH_2-$), 4.1 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 3.72 (6H, s, OCH_3 and $CH_3OSO_3^-$), 3.63 (3H, s, OCH_3), 3.43 (4H, bs, H_2O), 2.39 (3H, s, $C\underline{H}_3$-CO) [Found: C, 54.57; H, 5.83; N, 5.47. $C_{24}H_{30}N_2O_9S.\frac{1}{2}H_2O$ requires: C, 54.23; H, 5.88; N, 5.27%]; ν_{max} (cm^{-1}): 1695 (C=O), 1608 ($C=\overset{+}{N}$), 1565 and 1595 (C O stretch), 1240 (S=O); λ_{max} (nm): 203, 228(sh), 235(sh), 258, 326, 347.

N-*Acetamidopapaverinium iodide [(41), X = I].*-When the oil (1.5 g) from the previous experiment, prior to addition of methylation agent, was treated with ethanol (5 cm^3) and 55% aqueous hydrogen iodide, the title compound gradually separated out as yellow prisms

*The ^{1}H n.m.r. spectrum recorded at 130° C is considerably simplified and, for example, the *ABX* system of the C-1 substituent aryl protons is now clearly resolved: J_{AX} = 8 Hz, J_{BX} = 1.5 Hz.

(0.6 g), m.p. 175-176° C. ^{1}H n.m.r. (d^6-DMSO): 8.71 [1H, d, (J =7 Hz), H-3], 8.45 [1H, d, (J =7 Hz), H-4], 7.99, 7.95 (2H, 2 x s, H-5, H-8), 7.15 (1H, bs, H-2'), 6.92 [1H, d, (J = 8 Hz), H-5'], 6.80 (1H, bd, H-6'), 5.10 (2H, bs, CH_2), 4.12, 4.08 (6H, 2 x s, 2 x OCH_3), 3.77, 3.75 (6H, 2 x s, 2 x OCH_3), 2.31 (3H, s, $COCH_3$) [Found: C, 50.4; H, 4.95; N, 5.4. $C_{22}H_{25}N_2O_5I$ requires: C, 50.4; H, 4.8; N, 5.3%]; ν_{max} (cm^-): 3350-3550, 1710, 1604; λ_{max} (nm): 207, 254, 315, 348.

6,7-Dimethoxy-1-(3',4'-dimethoxybenzyl)-2-(N-methylacetamido)-1,2-dihydroisoquinoline (42).-6,7-Dimethoxy-1-(3',4'-dimethoxybenzyl)-2-(*N*-methylacetamido)-isoquinolinium iodide (200 mg) was suspended in absolute ethanol (4 cm^3) and sodium borohydride (14 mg) was added. The mixture was stirred at room temperature for 30 min, after which time the yellow colour of the iodide salt had disappeared. Water (100 cm^3) was then added and the product extracted into dichloromethane (3 x 25 cm^3). Removal of the solvent from the dry, combined extracts gave a solid (138 mg, 90%) which was chromatographically homogeneous (alumina/70% ethyl acetate in petrol; Rf = 0.5). Recrystallisation from ethanol afforded the title compound as colourless plates (105 mg, 69%), m.p. 167-168.5° C. ^{1}H n.m.r. δ(d^6-DMSO. temperature 150° C*): 6.77 [1H, bd, (J = ∿9Hz), H-5], 6.65 (1H, s, H-5 or H-8), 6.63-6.49 (2H, m, H-2', H-6'), 6.24 (1H, s, H-5 or H-8), 6.05 [1H, d, (J = 7 Hz), H-3], 5.69 [1H, d, (J = 7 Hz), H-4], 4.68 [1H, t, (J = 7 Hz), H-1], 3.77, 3.75, 3.69, 3.55 (4 x 3H, 4 x s, 4 x OCH_3), 2.79-3.00 (5H, m, NCH_3, CH_2), 1.89 (3H, s, $COCH_3$) [Found: C, 67.01; H, 6.88; N, 6.85. $C_{23}H_{28}N_2O_5$ requires: C, 66.97; H, 6.84; N, 6.79%]; ν_{max} (cm^-): 1660, 1620; λ_{max} (nm): 289, 307.

The isoquinolinium salt (500 mg) was also reduced with d^4-sodium borohydride (100 mg) under similar conditions to give the 1-deutero- analogue of (42) in a yield of 65% after recrystallisation from ethanol.

*At ambient temperature the ^{1}H n.m.r. spectrum is much more complex (see Figures 1-4, Chapter 2), indicating the existence of energy barriers to rotation and/or inversion.

Reduction of the 1,2-dihydroisoquinoline

Attempted further reduction with sodium borohydride.-(i) The 1,2-dihydroisoquinoline was generated *in situ* by treating an ethanolic suspension of the methiodide salt [(33), 0.1 g] with an excess of sodium borohydride (0.1 g) as described previously. Formation of the dihydropapaverine was judged to be complete after 5 min stirring at room temperature, by which time the yellow colour of the salt had been discharged. Instead of isolating the partially reduced isoquinoline at this point, the mixture was heated at reflux for 2 h. The usual work-up procedure afforded only the dihydropapaverine in a yield of 60%.

Attempted further reduction with sodium borohydride.-(ii) The dihydroisoquinoline [(42), 0.1 g] was suspended in *n*-butanol and sodium borohydride was added. The mixture was then heated at reflux for 5 h, during which the progress of the reaction was monitored by t.l.c. (30% ethyl acetate in petrol/alumina). No tetrahydropapaverine formation was observed during this time; the only detectable change being the gradual appearance of a baseline spot on the t.l.c. plate, presumably due to slow decomposition of the starting material.

Attempted reduction with sodium cyanoborohydride.-*N*-[*N'*-Methylacetamido]-1,2-dihydropapaverine (0.11 g) was suspended in ice-cold 0.1 M hydrochloric acid (5 cm^3) and an excess of sodium cyanoborohydride was added. The resulting mixture was stirred at room temperature for 22 h, during which t.l.c. analysis (60% acetone in petrol/silica) indicated that no reaction was taking place. Ethanol (5 cm) was added to increase the solubility of the 1,2-dihydroisoquinoline and the suspension was stirred for a further 24 h. Again t.l.c. analysis showed that none of the desired tetrahydropapaverine was present, although decomposition was occurring to give a number of products which were not identified.

Catalytic reduction.-(i) An ethanolic solution (280 cm^3) of *N*-[*N'*-methylacetamido]-1,2-dihydropapaverine was hydrogenated at 70 p.s.i. over palladium on charcoal catalyst for 22 h. Filtration through celite and evaporation yielded only starting material. The experiment was repeated at 200 p.s.i. for 48 h, but again, only starting material was recovered.

Catalytic reduction.-(ii) The 1,2-dihydroisoquinoline (40 mg) was dissolved in glacial acetic acid and the solution hydrogenated overnight at room temperature and pressure over a palladium on charcoal catalyst. The resulting mixture was filtered through celite and partitioned between water and dichloromethane. Basification with sodium carbonate and the separation and subsequent t.l.c. analysis of the organic phase revealed a number of products. The formation of side products in addition to the expected product rendered this method unsatisfactory.

Catalytic reduction.-(iii) Successful reduction was finally effected using Adams' catalyst - see 6,7-dimethoxy-1-(3',4'-dimethoxybenzyl)-2-(*N'*-methylacetamido)-1,2,3,4-tetrahydroisoquinoline (Method 4).

2-Amino-6,7-dimethoxy-1-(3',4'-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (49).-Papaverine (6.6 g) was aminated in the usual way and the resulting product dissolved in 95% aqueous ethanol (80 cm^3). Sodium borohydride (2 g) was added in portions and the effervescing mixture was stirred at room temperature for 5 min before pouring into 2 M hydrochloric acid. When all gas evolution had ceased, the solution was basified with 30% sodium hydroxide and extracted with dichloromethane (3 x 175 cm^3). The combined organic extracts were dried and evaporated down to give a pale-reddish oil which slowly crystallised. Trituration in ethanol afforded the title compound as a pure white powder (2.7 g, 72%), m.p. (ethanol) 112-113.5° C. ^1H n.m.r. ($CDCl_3$): 6.78-6.58 (3H, m, 2'-H, 5'-H, 6'-H), 6.52 (1H, s, 5-H), 6.13 (1H, s, 8-H), 3.81 (6H, s, 2 x OCH_3), 3.77, 3.59 (2 x 3H, 2 x s, 2 x OCH_3), 3.4-2.5 (9H, m, aliphatic protons + NH_2, integral height reduced by addition of D_2O to sample,

then equivalent to 7H) [Found: C, 67.39; H, 7.13; N, 7.79. $C_{20}H_{26}N_2O_4$ requires: C, 67.02; H, 7.31; N, 7.82%]; ν_{max} (cm^{-1}): 1610; λ_{max} (nm): 234, 283.

2-Acetamido-6,7-dimethoxy-1-(3',4'-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (46).-Method 1. 2-Amino-6,7-dimethoxy-1-(3',4'-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (0.98 g) in 95% ethanol (14 cm^3) and acetic anhydride (3 cm^3) were stirred at room temperature for 15 min. The solvent was removed under reduced pressure and the residual oil partitioned between dichloromethane and water. Sodium carbonate was then added until the well stirred mixture remained neutral to litmus. The organic phase was separated, dried and evaporated to give a pale-yellow oil. The oil was taken up in the minimum quantity of hot acetone and, upon cooling, the product crystallised out as colourless needles (0.8 g). The mother liquors were evaporated and the residue recrystallised to give a further crop (30 mg) of product and hence an overall yield of 0.83 g (76%), m.p. 138.5-139.5° C. ^{1}H n.m.r. (d^6-DMSO):* 9.00, 8.43 (2 x bs, integral ratio 1/2, 1H), 6.85-6.50 (5H, m, aryl protons), 4.18 [1H, bt, (J = ∿7 Hz), 1-H], 3.73 (9H, bs, 3 x OCH_3), 3.62 (3H, bs, OCH_3), 3.33-2.60 (7H, m, aliphatic protons), 1.85, 1.70 (2 x bs, integral ratio 1/2, CH_3CO); m/e 400 (M^+, 2), 339 (12), 249 (20), 247 (100) [Found: C, 66.03; H, 7.13; N, 7.06. $C_{22}H_{28}N_2O_5$ requires: C, 65.98; H, 7.05; N, 6.99%]; ν_{max} (cm^{-1}): 3245, 1658; λ_{max} (nm): 282.

Method 2. 2-Acetamido-6,7-dimethoxy-1-(3',4'-dimethoxybenzyl-isoquinolinium iodide (0.23 g), suspended in 98% ethanol (5 cm^3) was treated with sodium borohydride (0.3 g). After 45 min, the reaction mixture was acidified with 2 M hydrochloric acid, rebasified with sodium hydroxide and extracted with dichloromethane (3 x 15 cm^3). The combined extracts were evaporated to give an oil (0.15 g), which crystallised from acetone as colourless needles (0.1 g, 57%), m.p. 138-139° C.

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*At 150° C the spectrum is simplified and the signals at δ 9.00 and 8.43 and at δ 1.85 and 1.70 merge into singlets at δ 8.7 and 1.80 respectively.

6,7-Dimethoxyl-1-(3',4'-dimethoxybenzyl)-2-(N'-methylacetamido)-1,2,3,4-tetrahydroisoquinoline (34).-Method 1. The previous compound (0.4 g), in freshly distilled dry tetrahydrofuran (22 cm^3), was treated with sodium hydride (1.04 molar equivalent). After stirring for 1.5 h under an atmosphere of nitrogen, methyliodide (2 molar equivalents) was introduced and the reaction mixture stirred for a further 15 min. Water (1 cm^3) was then slowly introduced, most of the solvent was removed by evaporation and the residue was partitioned between brine and ethyl acetate. The organic layer was dried and evaporated to yield a pale-yellow oil which was chromatographed on silica eluting with 35% acetone in petrol (60-80° C) to give the title compound as a colourless oil, which slowly crystallised and was recrystallised from ethanol (0.17 g, 41%), m.p. 122-123° C. ^1H n.m.r. (d^6-DMSO): 6.95-6.60 (5H, m, aryl protons), 4.5-4.3 [1H, bt,* (J = 5.5 Hz), H-1], 3.8-3.5 (12H, 4 x s, 4 x OCH_3), 3.3-2.5 (6H, m, aliphatic protons), 2.88 (3H, s, NCH_3), 1.9 (3H, s, CH_3CO). [Found: C, 66.7; H, 7.3; N, 6.6. $C_{23}H_{30}N_2O_5$ requires: C, 66.65; H, 7.3; N, 6.8%]; ν_{max} (cm^{-1}): 1645; λ_{max} (nm): 282.

Because of the limited solubility of (46) in THF, the above method was only poorly reproducible. Other methods were therefore investigated.

Method 2. *Attempted N'-methylation using potassium fluoride on alumina as the base.*-Aluminium oxide (Fisons "Camag" - Brockmann type I - neutral, mesh size 100-200, 15 g) was mixed with potassium fluoride (10 g) in water (200 cm^3). The water was then removed at 50-60° C under reduced pressure to give the supported base as a colourless powder. 2-Acetamido-6,7-dimethoxy-1-(3',4'-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (117 mg) was dissolved in dry acetonitrile (10 cm^3) and methyliodide (0.035 cm^3) and the supported base (400 mg) added. The mixture was then stirred at room temperature overnight, after which time thin layer chromatographic analysis (silica/60% acetone in petrol) showed that most of the starting material

*The room temperature spectrum was not particularly well resolved. At 120° C the spectrum became much sharper and, for example, the fine structure of the triplet was clearer.

had been consumed. However, only a trace of the desired product was evident and the major product of the reaction remained at the baseline. No attempt was made to isolate this product.

Method 3. The acetamidoisoquinoline [(46), 588 mg] was dissolved in dry dichloromethane (6 cm^3) and the solution added carefully to a suspension of sodium hydride (42 mg) in a mixture of dichloromethane (12 cm^3) and dry dimethylformamide (4 cm^3). The resulting mixture was stirred at room temperature under an atmosphere of nitrogen until no further evolution of gas was observed (140 min). Methyliodide (0.5 cm^3) was then added and the solution was stirred for 10 min before pouring into water. The cloudy aqueous phase was washed once with dichloromethane and the combined organic layers were washed thoroughly with water (7 x 150 cm^3) before drying and evaporating. Traces of dimethylformamide were removed *in vacuo* with the assistance of a "cold finger" attachment maintained at liquid nitrogen temperature. The title compound was obtained as a chromatographically homogeneous (60% acetone in petrol/silica) colourless oil (550 mg, 90%). Crystallisation of the oil was achieved by dissolving in hot ethanol and chilling in a refrigerator for several weeks. The yield of crystalline product thus obtained was 288 mg (47%).

Method 4. 6,7-Dimethoxy-1-(3',4'-dimethoxybenzyl)-2-(*N*-methyl-acetamido)-1,2-dihydroisoquinoline (0.1 g) in ethyl acetate (50 cm^3) was hydrogenated at 250 p.s.i. pressure over platinum oxide catalyst (0.01 g) for 48 h. Removal of the solvent and catalyst gave the title compound as an oil which slowly crystallised (0.085 g, 85%).

Method 5. 6,7-Dimethoxy-1-(3',4'-dimethoxybenzyl)-2-(*N*'-methylacetamido)isoquinolinium methyl sulphate (0.2 g) in 98% ethanol (10 cm^3) was treated with sodium borohydride (10 cm) and the mixture heated at reflux for 1 h. Water (10 cm^3) was then added and the product tetrahydroisoquinoline isolated by extraction with dichloromethane (3 x 25 cm^3) , followed by the usual work-up procedure, yield 0.14 g (89%).

This reaction was found to be poorly reproducible with many attempts resulting only in formation of the 1,2-dihydroisoquinoline (42).

Attempted methylation of (34).-(i) Using methyliodide in acetone. The above compound (0.16 g) was dissolved in acetone (2 cm^3) and freshly redistilled methyliodide (0.5 cm^3) added. The solution was boiled for 7½ h before being allowed to cool to room temperature over the weekend. T.l.c. analysis (60% acetone in petrol/silica) showed that only starting material was present.

(ii) Using Meerwein's reagent. The methylacetamidoisoquinoline (0.117 g) was dissolved in dry dichloromethane and the solution was cooled to -15° C. The cold solution was subsequently added by syringe to a suspension of trimethyloxonium tetrafluoroborate (50 mg) in dry dichloromethane (5 cm^3) under a blanket of nitrogen. The mixture was then stirred at room temperature for 87 h, by which time the solution had acquired a brownish colour and only traces of the reagent remained visible. T.l.c. analysis showed that only a trace of starting material was present along with a highly fluorescent product(s) located at the baseline. The solvent was removed under reduced pressure to give a brown oil which showed no tendency to crystallise. The ^1H n.m.r. spectrum of this crude product was too poorly resolved to be of any use. Crystallisation was eventually achieved by treating the oil with hot ethanol and allowing to cool overnight and thus a crop (68 mg) of reddish-brown florets was obtained. The product was tentatively identified as 6,7-dimethoxy-1-(3',4'-dimethoxybenzyl)-2-methyl-2-[*N*'-methylamino]-1,2,3,4-tetrahydroisoquinoline (53). ^1H n.m.r. δ(d^6-DMSO): 9.72 [1H, bs (exchangeable), *N*'-H], 6.4-7.0 (5H, m, aromatics), 4.38 (1H, m, H-1), 2.4-3.8 (6H, m, aliphatic protons, overlapping with singlets due to methoxyl and *N*-methyl protons), 3.78 (12H, s, 4 x OCH_3), 3.62 (3H, s, $\overset{+}{N}$-CH_3), 2.65 (3H, s, *N*'-CH_3); m/e 219; ν_{max} (cm^{-1}): 3125, 3075, 1615, 1598.

6,7-Dimethoxyl-1-(3',4'-dimethoxybenzyl)-2-(N-phthalimido)-1,2,3,4-tetrahydroisoquinoline (50).-2-Amino-6,7-dimethoxyl-1-(3',4'-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (1 g) and phthalic anhydride (0.41 g) were heated in a Dean-Stark apparatus with dry toluene containing triethylamine (0.04 cm^3). After 2 h, the solvent was removed to yield a pale-brown gum which was chromatographed on

neutral alumina, eluting with 40% ethyl acetate in petrol (60-80° C), thus affording the title compound as a pale-yellow solid (0.84 g, 62%), which was recrystallised from ethanol, m.p. 142.5-144.5° C. ^{1}H n.m.r. δ($CDCl_3$): 7.72 (4H, s, protons of phthalimido unit), 6.85 (1H, bs, H-2'), 6.65 [1H, bd, (J = ∿8 Hz), H-6'], 6.62, 6.55 (2 x 1H, 2 x s, H-5, H-8), 4.46 [1H, d, (J = 8 Hz), H-5'], 5.30 (1H, m, H-1), 3.87, 3.82, 3.62 (12H, 3 x s, 4 x OCH_3), 3.90-2.40 (6H, m, remaining protons) [Found: C, 68.7; H, 6.1; N, 6.1. $C_{28}H_{28}N_2O_6$ requires: C, 68.8; H, 5.8; N, 5.7%]; ν_{max} (cm^{-1}): 1780, 1760, 1715; λ_{max} (nm): 281.

Attempted methylation of (50).-(i) Using methyliodide in acetone. An acetone solution of the phthalimido compound [(50), 1 g] and freshly redistilled methyliodide (3 cm^3) were heated together at reflux for 12 h. Removal of the solvent and residual reagent yielded a yellow crystalline solid which was shown to be starting material by i.r. spectroscopic and t.l.c. analysis.

(ii) Using methyliodide in acetonitrile. *N*-Phthalimidotetrahydropapaverine (1.22 g) was dissolved in a mixture of dry acetonitrile (10 cm^3) and methyliodide (3 cm^3) and the solution was heated at 60° C for 8 days, followed by a further 3 days at room temperature. The solution was then evaporated and the residue recrystallised to afford starting material (0.77 g).

(iii) Using dimethylsulphate in acetonitrile. The phthalimido compound [(50), 0.25 g] was dissolved in hot dry acetonitrile (3 cm^3) containing dimethylsulphate (0.05 cm^3). The solution was brought to reflux and maintained as such overnight. On cooling, crystals were deposited. These were identified as starting material by t.l.c. and i.r. comparison. Analysis of the mother liquors similarly showed only starting material.

2-Acetamido-6,7-dimethoxy-1-(3',4'-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolinium iodide (55).-The tetrahydrosioquinoline (46) (0.15 g) in warm acetone (3 cm^3) was treated with methyliodide (1 g) and the mixture was heated at reflux for 69 h. A colourless solid gradually formed and this was collected at the end of the reaction to give the title compound as an amorphous

powder (0.15 g, 73.8%), m.p. 186-187° C. ^{1}H n.m.r. δ(*d*^{6}-DMSO:$CDCl_3$ 2:1): 6.94-6.45 (5H, m, aryl protons),5.7 (1H, bs, NH), 4.15-3.2 (7H, m, aliphatic protons, overlapping with singlets due to methoxyl and N^+-methyl protons), 3.80, 3.78, 3.66, 3.63 (4 x 3H, 4 x s, 4 x OCH_3), 3.38 (3H, s, $N^+\underline{CH_3}$), 2.18 (3H, s, $CO\underline{CH_3}$) [Found: C, 50.6; H, 5.8; N, 5.2. $C_{23}H_{31}N_2O_5I$ requires: C, 50.9; H, 5.8; N, 5.2%]; m/e (7%): 414.2158 [$C_{23}H_{30}N_2O_5$ (M^+-HI) requires: 414.2156], 101 (100%): $C_4H_9N_2O$.

Photolysis of 2-acetamido-6,7-dimethoxy-1-(3',4'-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolinium iodide.-The salt (50 mg) was dissolved in methanol (100 cm^3) and the solution was irradiated for 3 h through a quartz immersion well with a medium pressure u.v. source. During the course of this time the reaction was monitored by withdrawing samples for t.l.c., mass spectrometric and u.v. spectroscopic analyses. Although the starting material was gradually consumed (change in u.v. spectrum), there was no evidence for the production of *O*-methylflavinantine [R_F 0.2, silica 60% ethyl-acetate/petrol (60-80° C)], although veratraldehyde [R_F 0.9 (same conditions)] was detected after a 15 min irradiation.

At the end of the reaction the solvent was removed and half of the residue partitioned between ethyl acetate and 0.2 *N* sodium hydroxide solution. The organic phase was evaporated and subjected to t.l.c. and mass spectrometric analyses. Again, no *O*-methyl-flavinantine was detected, although the presence of veratraldehyde was confirmed by comparison with an authentic specimen after the residue had been purified by chromatography on silica. The remaining crude photolysis product was dissolved in 98% aqueous ethanol and heated with sodium borohydride; after evaporation of the solvent, the residue was treated with warm 2 *N* sodium hydroxide and extracted with ethyl acetate. The solvent was removed and the residue (15 mg) subjected to mass spectrometric analysis. M/e E1 (%): 207 (34), 206 (38), 195 (29), 168 (100), 166 (32), 165 (30), 164 (67), 151 (39), 139 (39). At low ionisation voltage (15 eV), only ions at m/e 207 and 168 are observed. Calc. for: 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline ($C_{12}H_{17}NO_2$) M^+ 207.1259; Found: 207.1264. Calc. for: veratryl alcohol ($C_9H_{12}O_3$) M^+ 168.0786; Found: 168.0787.

6,7-Dimethoxy-1-(3',4'-dimethoxybenzyl)-2-nitroso-1,2,3,4-tetrahydroisoquinoline (61).-Tetrahydropapaverine hydrobromide (1 g) in 50% aqueous ethanol (20 cm^3) was treated with several drops of 2 *M* hydrochloric acid. A cold solution (~5° C) of sodium nitrite (0.24 g) in water (10 cm^3) was introduced into the reaction vessel and the mixture was stirred for 5 min at room temperature, prior to warming to 60° C for 20 min. After this time, the resulting colourless precipitate was collected, washed several times with water and dried under reduced pressure at 60° C to afford the title compound, m.p. 131° C (0.66 g, 61%). ^{1}H n.m.r. (d^6-DMSO): 6.9-6.55 (5H, m, aromatic protons), 6.05-5.80 (1H, 2 x t,* 1-H), 4.6, 4.05 (2H, 2 x m,* $3H_2$), 3.89, 3.82, 3.75, 3.70 (4 x 3H, 4 x s, 4 x OCH_3), ~3.75, 2.90 (1H, 2 x m, 4-H_{ax}, integral ratio 1:1), 3.40, 3.10 (2H, 2 x m, $C\underline{H}_2Ar$ integral ratio 1:1), 2.65 (1H, m, 4-H_{eq}): ν_{max} (cm^{-1}): 1615, 1598, 1470; λ_{max} (nm): 228, 280. When the spectrum is re-run at 120° C, the signals marked with an asterisk are sharpened, but coalescence of the resonances is still not effected. In simple *N*-nitrosamines[13-15] E_{act} = 20-25 kcal mol^{-1}, but in our compound this barrier is much higher and a detailed analysis of the ^{1}H n.m.r. spectrum suggests the existence of diastereoisomerism as a result of the chiral centre at C-1 and restricted rotation with the *N*-nitroso group. M/e El (%): 342 (21), 191 (46), 151 (100); CI 373 (M+1, 72) [Found: C, 64.3; H, 6.5; N, 7.5. $C_{20}H_{24}N_2O_5$ requires: C, 64.5; H, 6.5; N, 7.5%].

Photolysis of 6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-2-nitroso-1,2,3,4-tetrahydroisoquinoline (61).-The nitroso compound (0.1 g) was dissolved in methanol (100 cm^3) containing concentrated hydrochloric acid (2 cm^3) and irradiated with a 125 W ultraviolet light source. After 13 h, during which time the progress of the reaction was carefully monitored bt withdrawing samples for t.l.c., g.l.c. and mass spectrometric analysis, the solvent was removed, the residue basified and extracted with diethyl ether. Chromatography of the extract over neutral alumina using with diethyl ether:petrol (60-80° C) mixtures eventually afforded veratraldehyde (10 mg) and 6,7-dimethoxy-3,4-dihydroisoquinoline (5 mg), m.p. (of picrate) 200-201° C, (lit.,[11] 201-203° C, identical with authentic samples, together with several

multicomponent oils (total weight 25 mg). Mass spectrometric analysis of basified crude reaction mixture (El) shows m/e 166 (veratraldehyde), 191 (6,7-dimethoxy-3,4-dihydroisoquinoline). CI spectrum exhibits m/e 167 and 192.

8,9-Dimethoxy-1-(3',4'-dimethoxyphenyl)-2-methylpyrazolo[5,1a]-isoquinoline (64).-Papaverine (1.4 g) was *N*-aminated and acetylated in the usual way. The product was then dissolved in methanol (25 cm^3) and the cooled solution treated with an excess of freshly prepared diazomethane in diethyl ether. After 12 h, the solvents were removed under reduced pressure to yield an oil which was taken up in the minimum of hot absolute ethanol (~3 cm^3) and the solution allowed to cool overnight. The following day, the title compound was collected by filtration as a colourless crystalline solid (0.17 g, 10%). The mother liquors were evaporated down and the residue partitioned between water and dichloromethane. Removal of the solvent from the organic phase and treatment of the resulting gum with ethanol and hydriodic acid, yielded golden-brown crystals of *N*-acetamidopapaverinium iodide (0.45 g, 21%). The aqueous layer was evaporated and similarly treated with hydriodic acid, but no further crop of crystals was obtained.

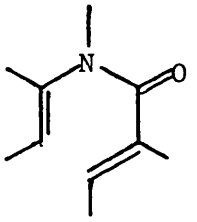
The analytical and spectroscopic details of the pyrazole are as follows: m.p., 181-182° C (ethanol). (250 MHz) ^1H n.m.r. δ(d^6-CH_3COCH_3): 8.15 [1H, d, (J = 7.5 Hz), H-5], 7.28, 7.23 (2 x 1H, 2 x s, H-7, H-10), 7.14 [1H, d, (J = 8 Hz, H-5'], 7.06 [1H, d, (J = 2 Hz), H-2'], 7.02 [1H, dd, (J_1 = 8 Hz, J_2 = 2 Hz), H-6'], 6·99 [1H, d, (J = 7.5 Hz), H-6], 3.90 (2 x 3H, 2 x s, 2 x OCH_3), 3.48 (3H, s, OCH_3), 2.30 (3H, s, NCH_3); m/e 378.1581 ($C_{22}H_{22}N_2O_4$ requires: 378.1579) [Found: C, 69.8; H, 6.2; N, 7.5. $C_{22}H_{22}N_2O_4$ requires: C, 69.7; H, 6.1; N, 7.4%]; ν_{max} (cm^{-1}) (KBr): 1502, 1480; λ_{max} (nm): 237, 256, 313, 328, 344.

CHAPTER 4

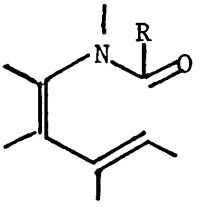
DIENAMIDE PHOTOCYCLISATIONS

4.1 Introduction

For the purposes of this discussion, dienamides may be considered as members of that class of compounds in which an amide unit is in conjugation with two carbon-carbon double bonds. The arrangement of greatest relevance to the work described within this chapter is that of the enacylenamine (73), with one carbon-carbon double bond at either side of the amide linkage, although dienamides (74) with a terminal amide function will be referred to briefly.



(73)



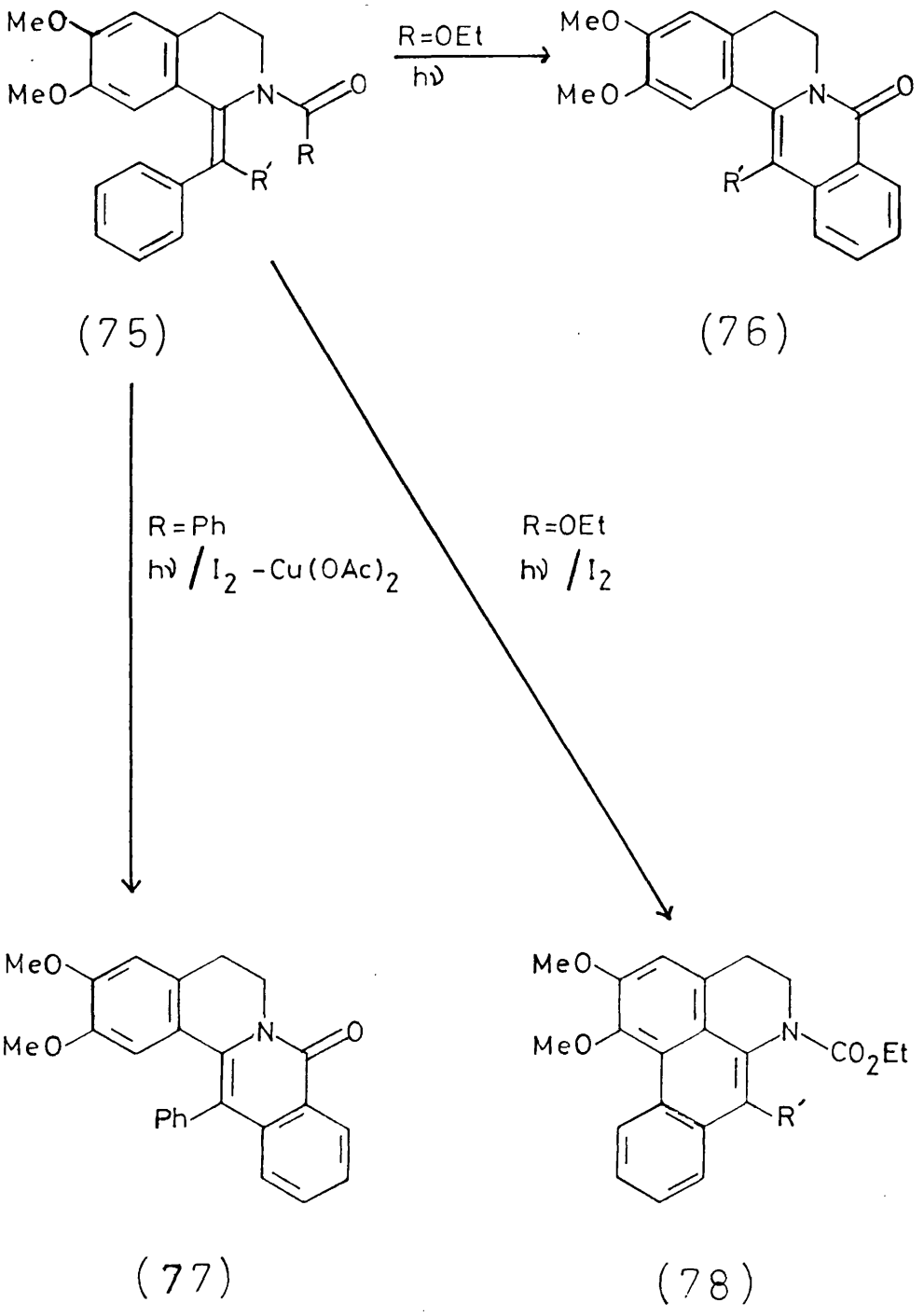
(74)

It has been known for a number of years that irradiation of dienamides with ultraviolet (u.v.) light results in cyclisation to pyridone derivatives of varying degrees of unsaturation. This cyclisation is analogous to the hexatriene-cyclohexadiene and stilbene-phenanthrene ring closures[64] and makes use of the considerable double bond character of the amide carbon-nitrogen linkage[55] in place of one of the formal double bonds of the stilbene triene system.

Due largely to the efforts of such workers as Ninomiya[65] and Lenz,[66] the dienamide cyclisation has been developed into a synthetic tool of considerable importance, particularly with respect to the synthesis of natural products. Examples of the application of this method will be given later.

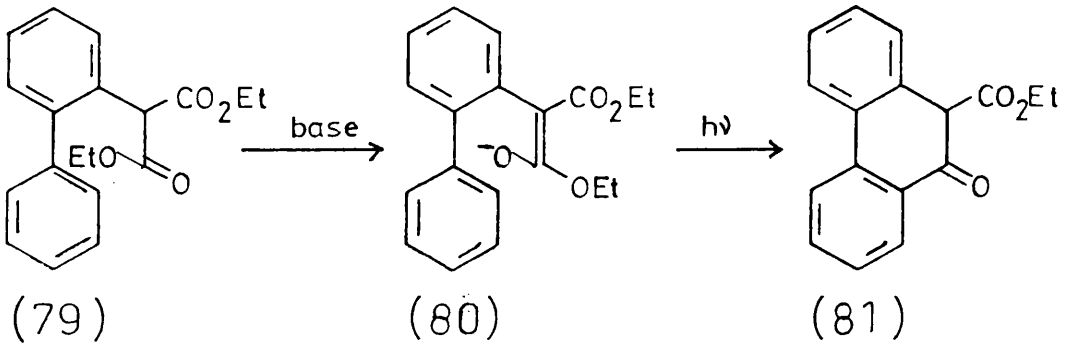
The dienamide cyclisation was discovered independently by two groups of workers, both of whom were investigating the synthesis of aporphines *via* cyclisation of stilbene enamides of the type (75) shown (see Scheme 20).

Lenz *et al.*[67] noted that during the oxidative photocylisation of the benzylidenetetrahydroisoquinoline [(75), R = OEt] to the dehydroaporphine (78), an oxyprotoberberine (76) was formed as a minor product. This side product became the major component of the reaction


MeO
MeO
N
O
R
R'
R=OEt
hν
(75)
(76)
R=Ph
hν / I2 -Cu(OAc)2
R=OEt
hν / I2
Ph
CO2Et
(77)
(78)

Scheme 20

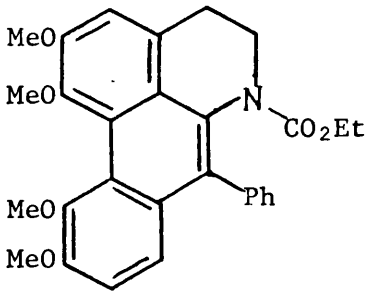
mixture in the absence of an oxidising agent. It was not clear at this point whether the formation of the oxyprotoberberine occurred *via* a concerted electrocyclic process, or whether it was simply a case of intramolecular photoacylation brought about by attack of the electron rich *ortho* position of the u.v. excited stilbene unit[68] upon the ester. A subsequent experiment[69] in which the malonic ester derivative (79) would not cyclise photochemically unless the enolate (80) was formed through treatment with base, indicated that the photoacylation could have occurred by a 6π-electrocylic reaction (Scheme 21).



(79) (80) (81)

Scheme 21

Shortly after Lenz's original discovery, Cava and Havlicek[70] reported that when *trans*-1-benzylidene-2-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(75), R = Ph, R' = H] was irradiated in ethanol containing iodine and cupric acetate, a 50% yield of the oxyprotoberberine (77) was obtained. In this case, although more than one mode of ring closure was possible, dienamide cyclisation was shown to occur in preference to the stilbene ring closure. Interestingly, when the bis-phenyl derivative [(75), R = OEt, R' = Ph], which is set up for competition between stilbene cyclisation and photocylation, was irradiated the 7-phenyldehydroaporphine (82) was obtained as the major product, thereby demonstrating that stilbene photocylisation predominates in this instance.



(82)

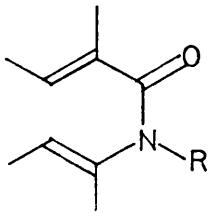
4.2 The mechanism of the dienamide cyclisation

Ninomiya[65] has classified dienamide cyclisations into four types, depending on whether or not the enacyl double bond and enamine double bond form part of an aromatic system (Scheme 22). To this list may be added a fifth type not mentioned by Ninomiya; namely the *N*-acylstyrylamines. This classification will be useful when describing the photochemical synthesis of alkaloids and will also help in the rationalisation of some of the finer points of mechanistic interest.

It is generally accepted that the dienamide ring closure is a concerted 6π-electrocyclic process, although it seems that cyclisation may take place from either a singlet or a triplet excited state. Ogata *et al.*[71] have investigated the photocyclisation of a number of acrylanilides and have found that addition of 1,3-pentadiene, a known triplet quencher, does not inhibit the reaction. Addition of the triplet sensitisers acetophenone (E_t = 73.6 Kcal mol^{-1}) and benzophenone (E_t = 68.5 K cal mol^{-1}) also has no effect. On the basis of this evidence they proposed that cyclisation occurs from the lowest excited singlet state S_1. The observation of a bathochromic shift of the fluorescence emission spectrum in polar solvents indicated that the S_1 state is due to a $\pi \rightarrow \pi^*$ transition. Witkop *et al.*[72] obtained a different result when they irradiated a benzene solution of the benzthiophene anilide (83) in the presence of 1,2-cyclohexadiene. Cyclisation to the fused dihydrobenzthiophene (84), which takes place readily in the absence of the triplet quencher, was suppressed and a linear Stern-Volmer plot was observed up to a concentration of 0.1 *M* of the quenching agent. These observations suggest that cyclisation of the anilide is taking place *via* a triplet excited state.

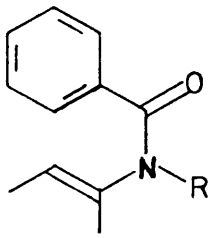
Scheme 22

Ninomiya's classification of dienamides



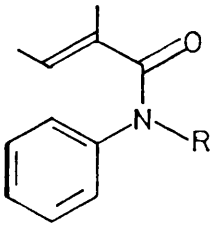
I

N-acryloylenamine



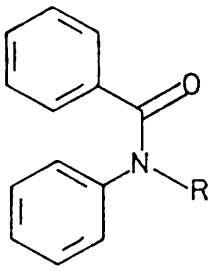
II

N-benzoylenamine



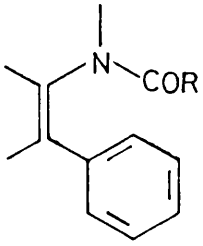
III

N-acryloylanilide



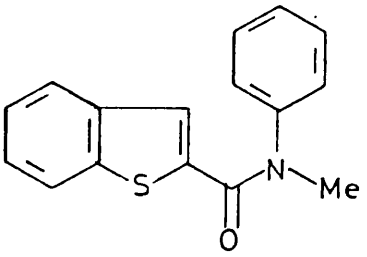
IV

benzanilide

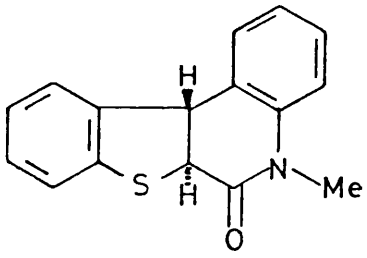


V

N-acylstyrylamine



(83)

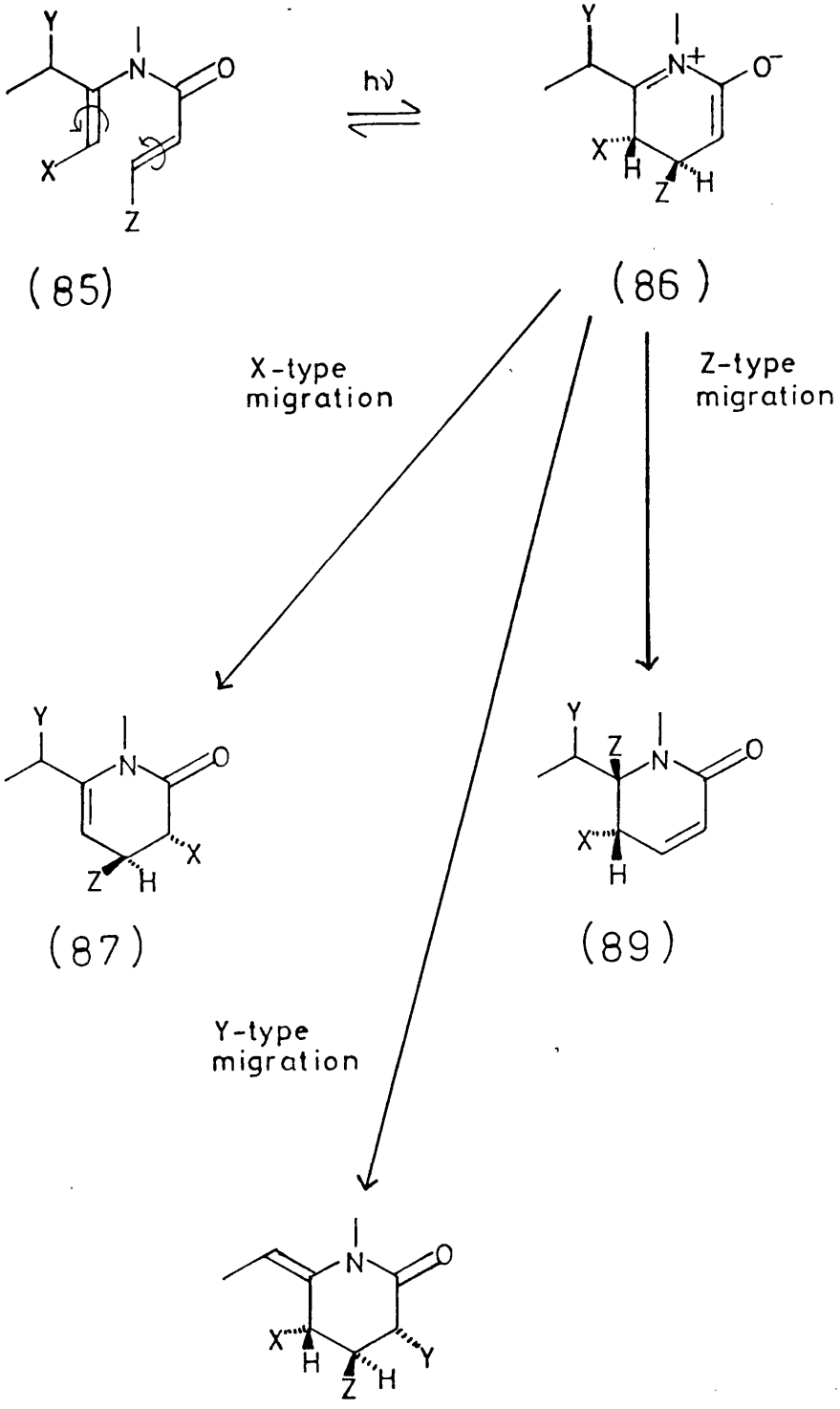


(84)

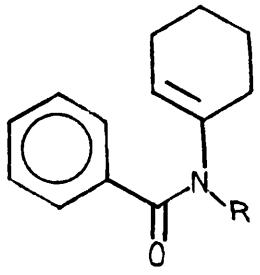
For a 6π-electron concerted cyclisation from the excited state, the Woodward-Hoffmann[73] rules require ring closure to occur in a con-rotatory fasion to give a species (86) in which the substituents about the newly formed bond are in the *trans* configuration (Scheme 23). The intermediate (86) which is presumed to be in photo-equilibrium with the ring opened form (85), is not an isolable entity and further irreversible transformation to a stable product must take place if subsequent ring opening is to be prevented.

This further transformation generally takes the form of a thermally allowed suprafacial [1,5]-sigmatropic shift although, depending on the nature of the system, deprotonation-reprotonation or elimination of substituents to give an aromatic system may occur instead.

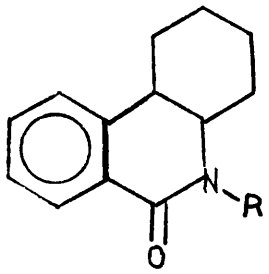
There are several positions from which [1,5]-sigmatropic migration may take place (Scheme 23); which substituent migrates depends to a large extent on whether or not migration will result in the re-establishment of an aromatic system. For instance, initial cyclisation of the *N*-benzoylenamine (90) is followed by a [1,5]-sigmatropic shift of type Z to re-establish the aromaticity of the benzene ring in the 3,4-dihydroisocarbostyril derivative (91). Migrations of type Z have not yet been recognised in simple acryloylenamines.


hν
(85)
(86)
X-type migration
Z-type migration
Y-type migration
(87)
(89)

Scheme 23



(90)



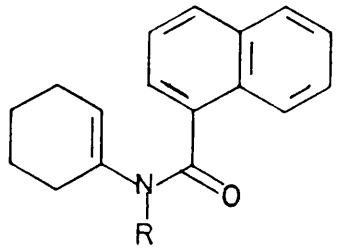
(91)

In contrast to the *N*-benzoylenamines, the lower resonance energy of the naphthalene ring system compared with that of two separated benzene rings means that the regaining of aromaticity is not such a strong driving force with the cyclisation products of *N*-naphthoylenamines. For example, irradiation of the *N*-(1-naphthoyl)-enamine (92) results in formation of some of the X-type migration product (93), whereas the *N*-(2-naphthoyl)enamine (94) gives rise to a 22% yield of the Y-type migration product (95).

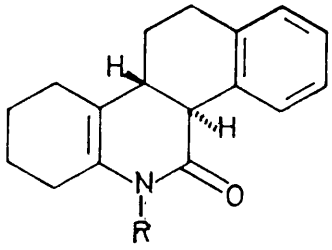
The first evidence in support of the [1,5]-sigmatropic shift was provided by Cleveland and Chapman[74] through their cyclisation of the acryloyl-2,4,6-trideuteroanilide (96). Exposure of this compound to u.v. light resulted in the incorporation of deuterium at the 3-position of the product (Scheme 24). However, irradiation of the *N*-deuteroanilide not bearing deuterium atoms in the aromatic ring also led to the appearance of deuterium at C-3 in the resulting dihydroisoquinolone. There are several possible explanations for this behaviour. Least likely, on steric grounds, is the proposal that successive [1,3]-sigmatropic shifts from C-5 to nitrogen and from nitrogen to C-3 are taking place, with loss of the isotope label being attributed to proton exchange at the nitrogen. A more feasible alternative is that [1,5]-sigmatropic migration is in competition with a protonation-deprotonation mechanism, whereby loss of deuterium from C-5 to re-establish the aromaticity of the benzene ring is balanced by protonation of the enolate at C-3 to give the product (98).

Conclusive evidence for a [1,5]-sigmatropic shift was put forward by Lenz,[75] who demonstrated that irradiation of the perdeuterobenzoylenamine (99) resulted in quantitative transfer of a deuterium atom to the expected position in the resulting oxyprotoberberine (100).

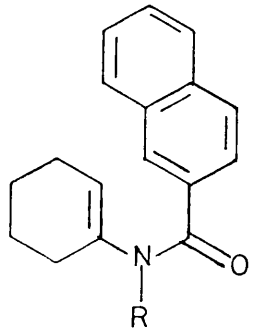
Groups other than hydrogen or deuterium have also been observed to migrate. Ninomiya[76] has successfully cyclised a number of *ortho*-substituted type II dienamides (101) and has observed that a methoxy group will migrate, whereas electron withdrawing groups such as the ester function will not (Scheme 25). Small yields of the products (104) formed by elimination of the substituents were also obtained



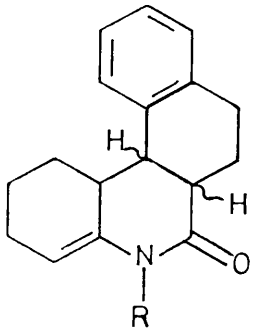
(92)



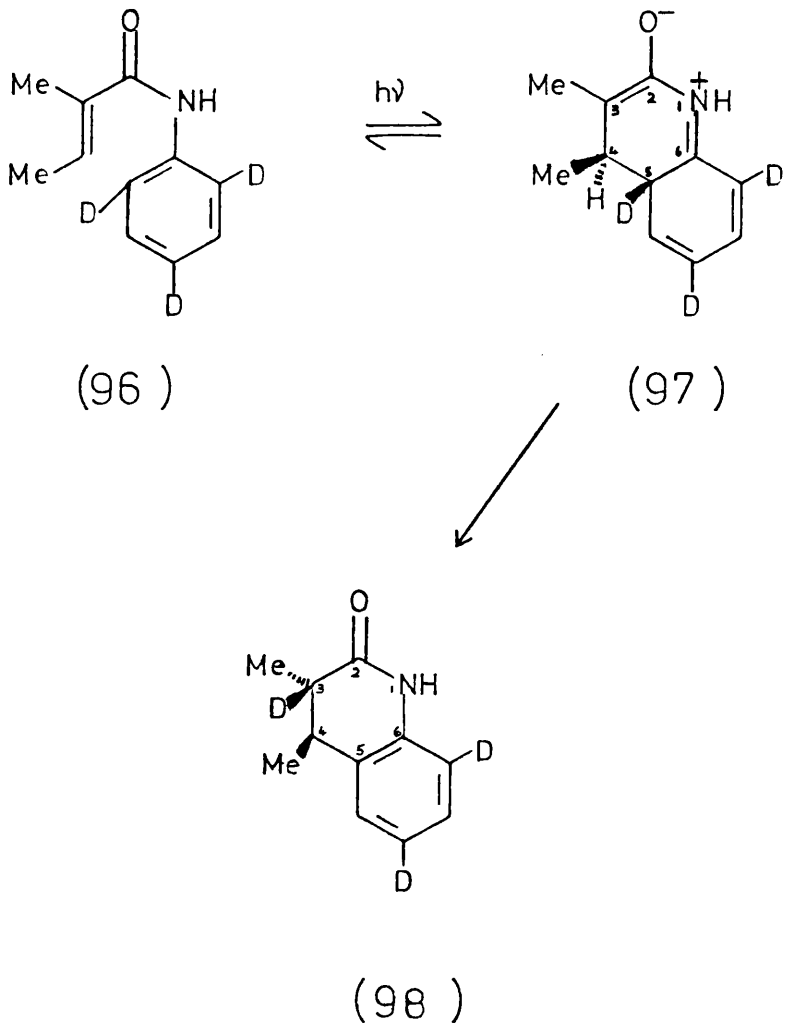
(93)



(94)

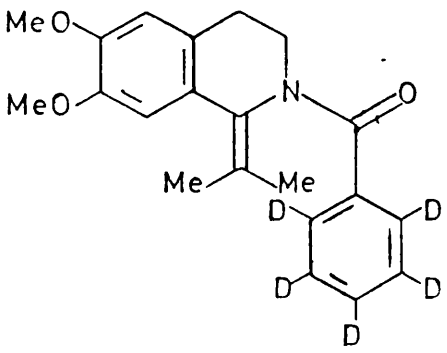


(95)

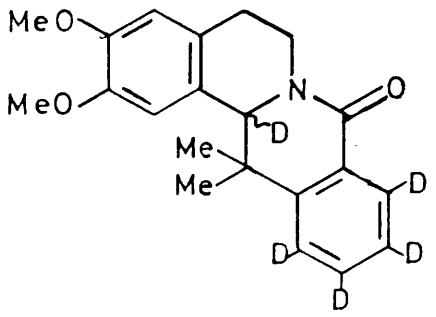


Scheme 24

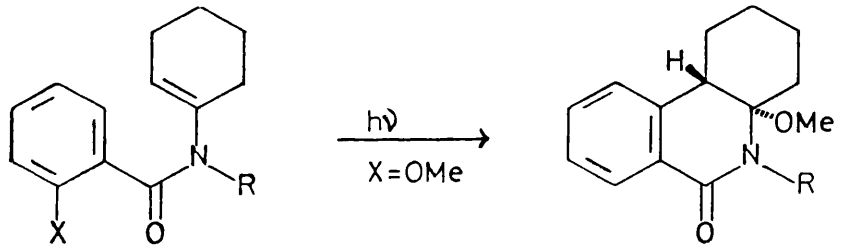
although, in the case of the methoxy group, it was not possible to say whether elimination occurred after, or instead of, migration.



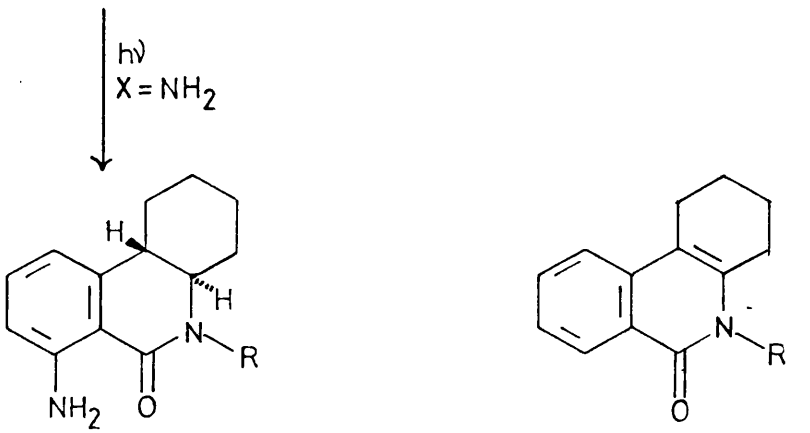
(99)



(100)



(101) (102)

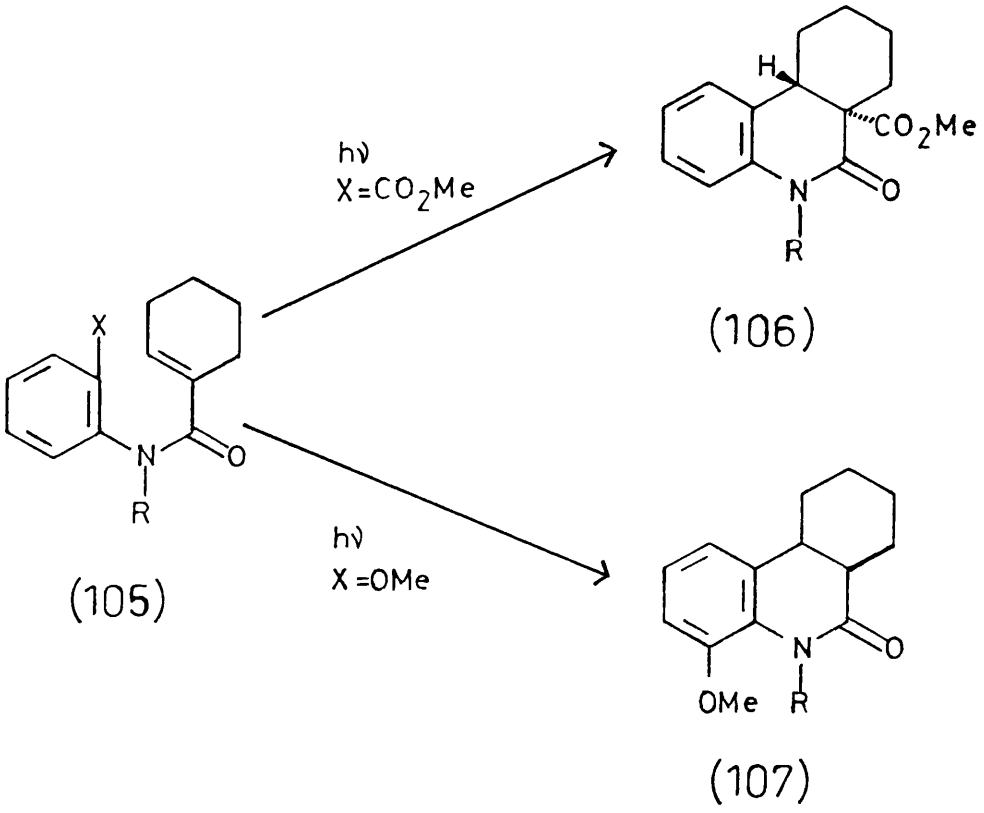


(103) (104)

Scheme 25

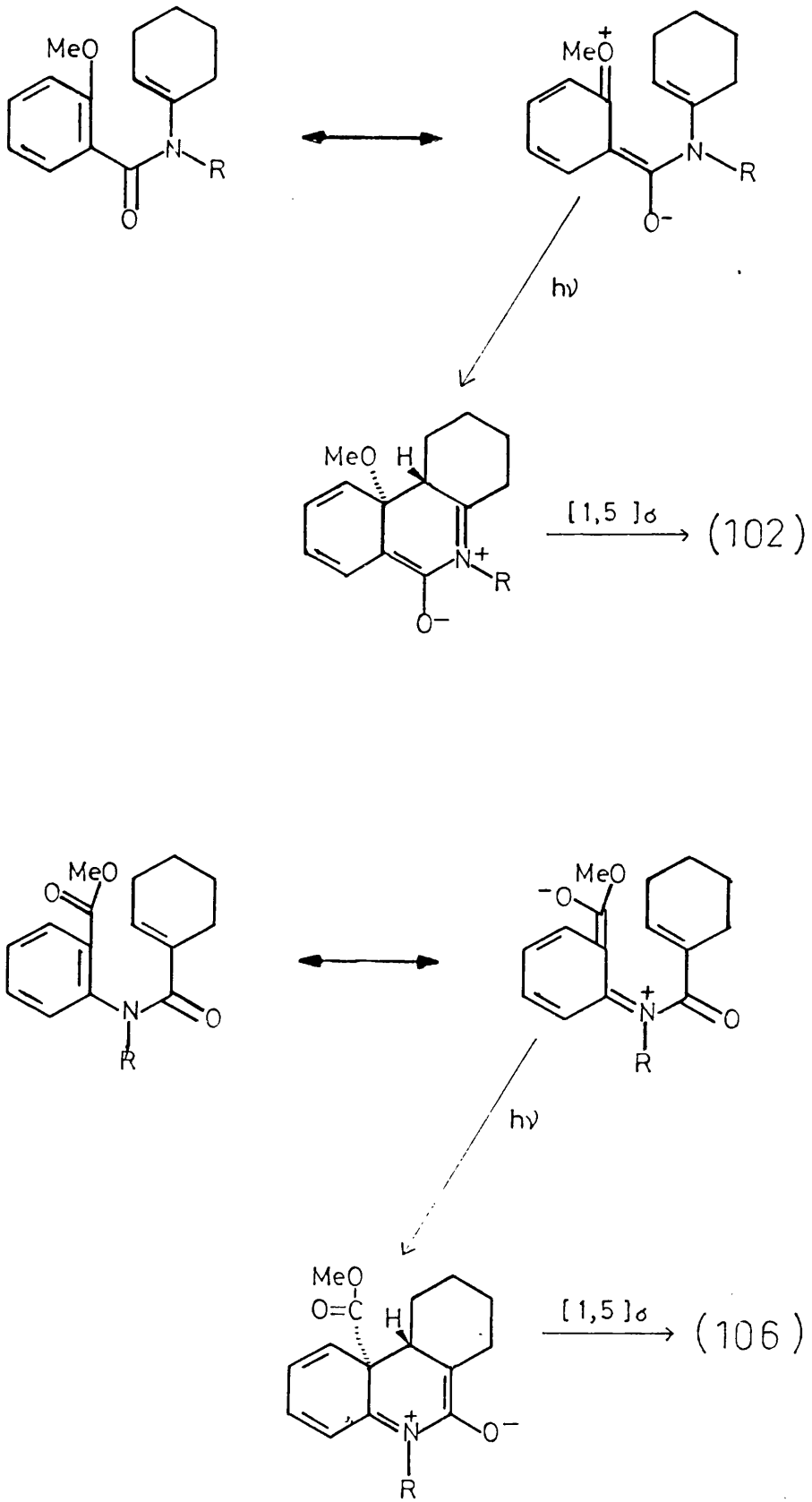
The reluctance of the amino group to undergo migration has been attributed to hydrogen bonding with the amide carbonyl which holds the molecule in the correct conformation for cyclisation at the unsubstituted *ortho* position.

Interestingly, when *ortho*-substituted type III dienamides (105) of the type shown in Scheme 26 were irradiated, migration of the methoxy group was not observed, whereas the carbomethoxy group did migrate on this occasion.

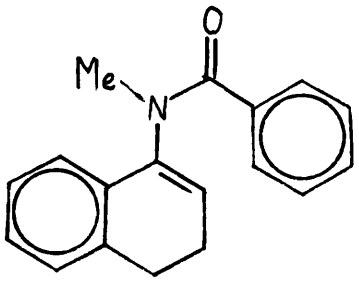


Scheme 26

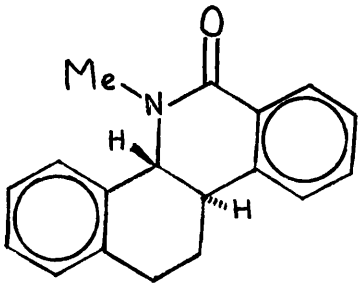
These differences in reactivity have been interpreted in terms of the polarising effects of the substituents on the dienamide system (Scheme 27).


MeO
N
R
O
MeO
N
R
O⁻
hν
MeO H
N⁺
R
O⁻
[1,5]σ
(102)
MeO
O
N
R
O
MeO
-O
N⁺
R
O
hν
MeO
O=C H
N⁺
R
O⁻
[1,5]σ
(106)

Scheme 27



(108)

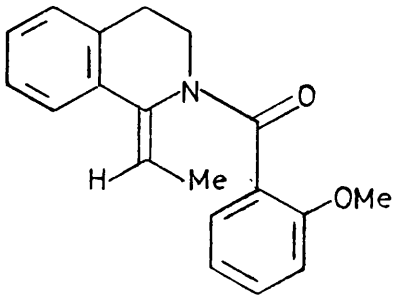


(109)

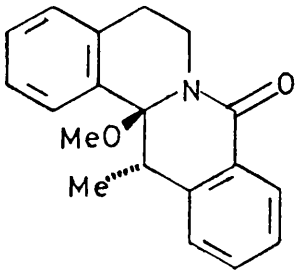
The migration of groups such as $CONH_2$, CH_3CO and CN has also been observed, but yields of migration products were low and were accompanied by elimination products.[77] Elimination of substituents such as Br, Cl, OCH_3 and $OCOCH_3$ has been reported by Lenz[78] and Kametani[79] although, in these instances, no evidence was obtained to indicate that a [1,5]- shift had taken place before elimination.

The [1,5]-sigmatropic shift of hydrogen must occur suprafacially as the antarafacial migration is prohibited on steric grounds. The postulated *trans* relationship of the substituents about the newly formed bond in the initial cyclisation product will therefore be reflected in the stereochemistry of the final product after sigmatropic migration has taken place.

Accordingly, irradiation of the *N*-benzoylmethylenamine (108) of α-tetralone furnished the *trans*-tetrahydrophenanthridone (109) in 55% yield.[80] Similarly the 2-methoxybenzoylenamine (110), the stereochemistry of which was established by nuclear Overhauser effect studies, cyclised such that the methyl and methoxy groups in the product (111)

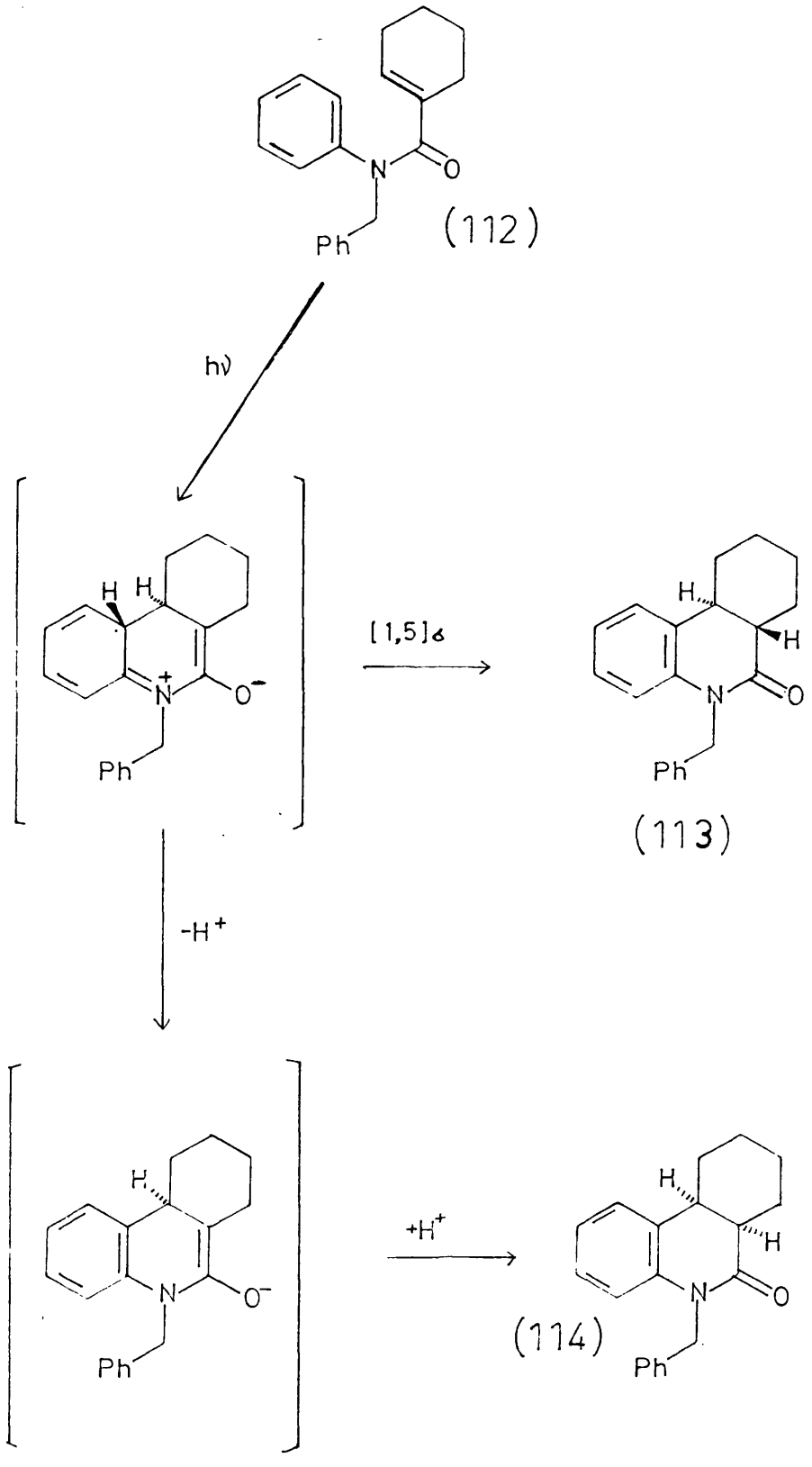


(110)



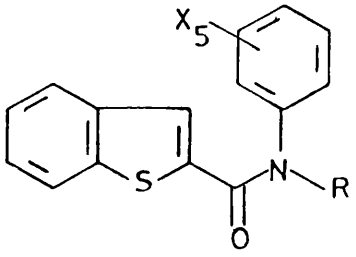
(111)

were *trans* orientated.[81] However, a mixture of *cis*- (114) and *trans*- (113) products was obtained when the acryloylanilide (112) was subjected to u.v. irradiation (Scheme 28).[82] It was postulated that this was due to a "partitioning" of the intermediate such that [1,5]-sigmatropic

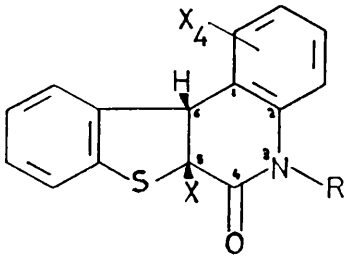


Scheme 28

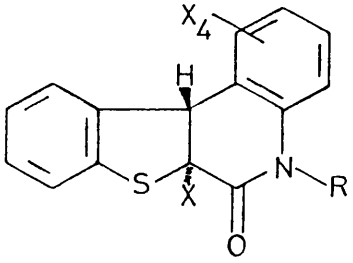
migration gave rise to the *trans*- product, whereas competing deprotonation-reprotonation led to the thermodynamically more stable *cis*-isomer. Proof of the existence of this alternative type of mechanism was provided by Kanaoka *et al.*[72] The photochemical ring closure of benzthiophene carboxanilide [(115), R = H] afforded the *cis*-dihydrobenzthiophene derivative [(116), R = H], while the *N*-methyl analogue [(115) R = CH_3] gave mainly the *trans* fused cyclised product [(117), R = CH_3]. When the anilide [(115), X = H, R = CH_3]



(115)



(116)

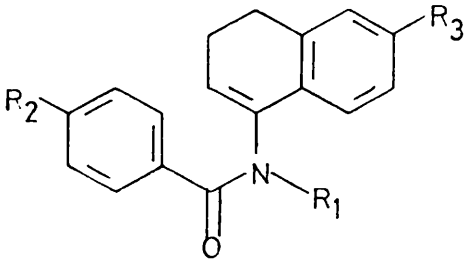


(117)

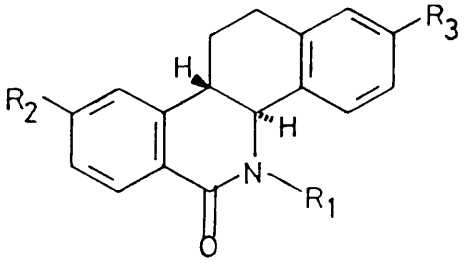
was irradiated in solvent containing deuterium oxide, the *cis*- product [(116), R = CH_3, X_4 = H , X = D] was obtained with deuterium incorporated at C-5, thereby indicating that exchange with the solvent was taking place. In comparison, irradiation of the perdeuteroanilide [(115),

$X_5 = D_5$, R = CH_3) gave the deuterium incorporated *trans* product [(117), X = D, R = CH) as the major product whilst the attendant *cis*-isomer showed no evidence of intramolecular deuterium transfer; the label instead being lost to the solvent.

In systems which favour a *cis* ring junction, photoisomerisation from the *trans*-isomer may sometimes occur. Irradiation of *para*-cyano- or carbomethoxy-benzoylenamines (118) of α-tetralone initially results in formation of a *trans* fused product (119) which undergoes quantitative conversion to the *cis* fused product (120) upon further

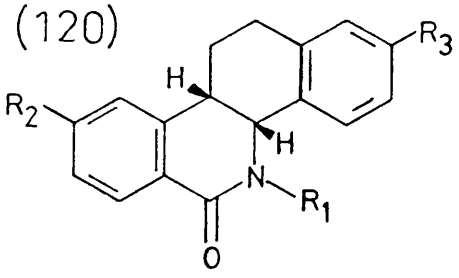


(118)



(119)

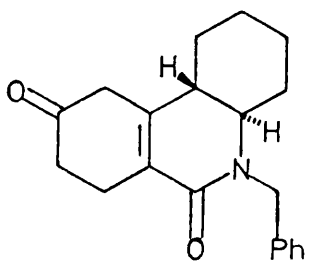
(120)



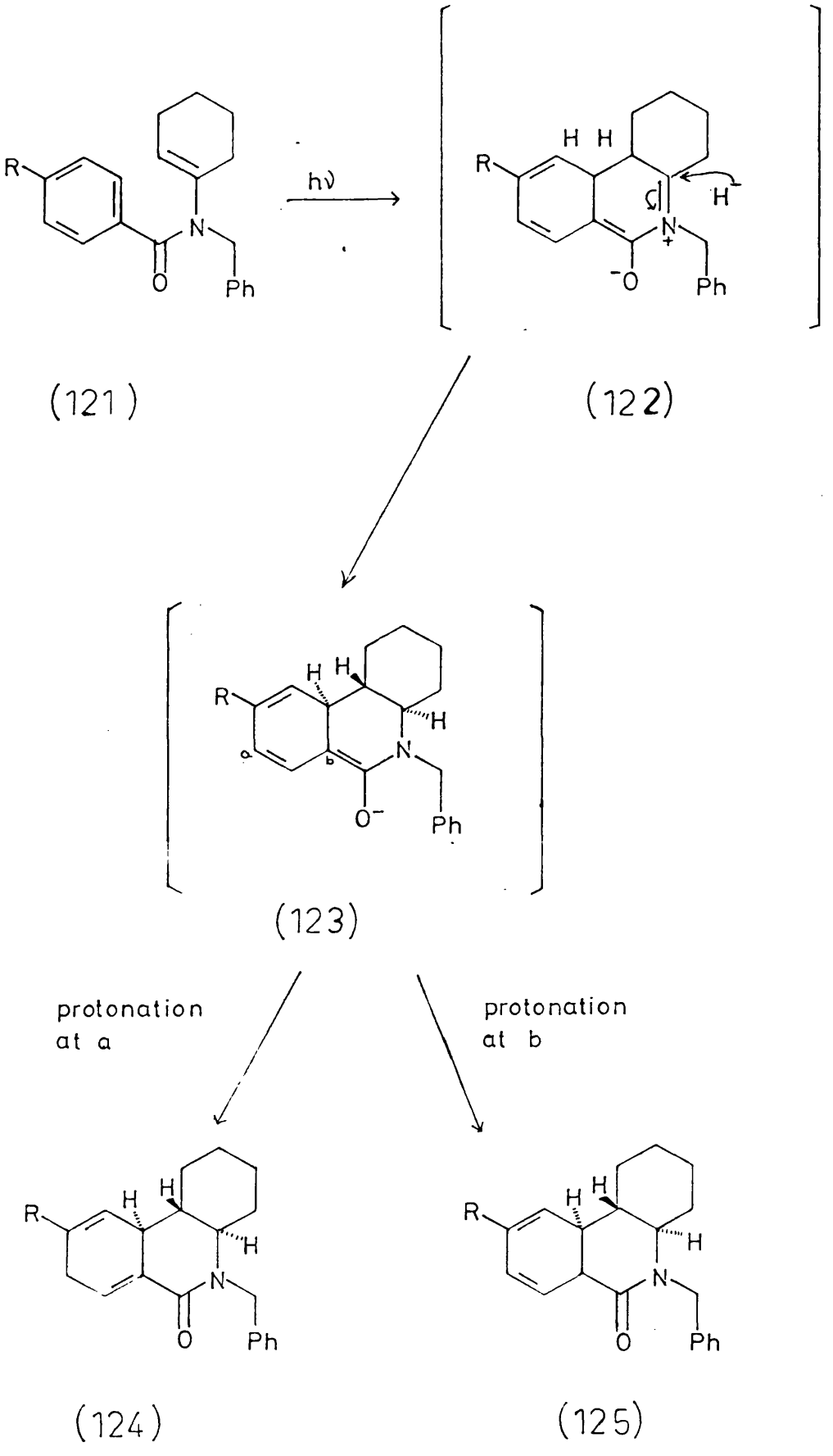
exposure to u.v. light.[83] That the mechanism of the isomerisation involves exchange with the solvent was indicated by deuterium incorporation studies. It was also found that the interconversion only

occurred in protic solvents such as methanol. Electron donating substituents at the *para*- position of the benzoyl moiety, or electron withdrawing groups at the *meta*- position, prevent this isomerisation from taking place. The unsubstituted derivative isomerises very slowly to give a 10% yield of *cis*- product after ten days. Conversion of *trans*-isomers to the *cis*- orientation has also been observed when the tetrahydrophenanthridone (109) is heated with selenium. Aromatised product is also obtained in this case.[80]

Further indications as to the nature of the transition state in the dienamide photocyclisation have been obtained by carrying out photolyses in the presence of a reducing agent. For example, Ninomiya[84] has recently carried out the photolysis of the type II dienamide (121) in the presence of sodium borohydride to yield the dienes (124) and (125) in 43% and 11% yield respectively. The formation of these products may be rationalised in terms of the hydride reagent attacking the 5- position of the intermediate (122) (see Scheme 29). Protonation of the "trienolate" (123) may then take place at either position *a* or position *b* to form the dienes, which will aromatise readily when heated in benzene. In addition to providing information about the nature of the transition state, this reaction is also of some synthetic importance. For instance, photolysis of a *para*-methoxybenzoylenamine [(121), R = OCH_3] in the presence of a reducing agent results in formation of the methoxy-diene [(125), R = OCH_3] which can be cleaved readily to give the ketone (126). A similar result is obtained when the 1-methylene-2-benzoyltetrahydroisoquinoline (127) is reductively photocyclised.

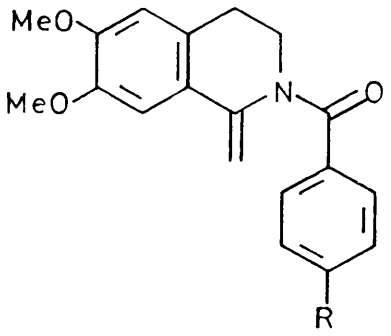


(126)

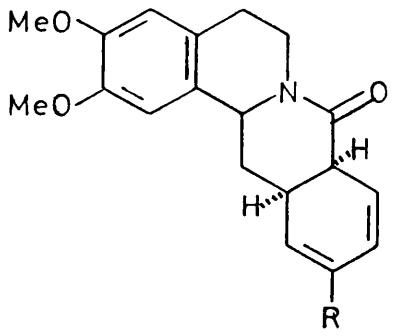

R
hν
O
N
Ph
H H
H
(121)
(122)
(123)
protonation
at a
protonation
at b
(124)
(125)

Scheme 29

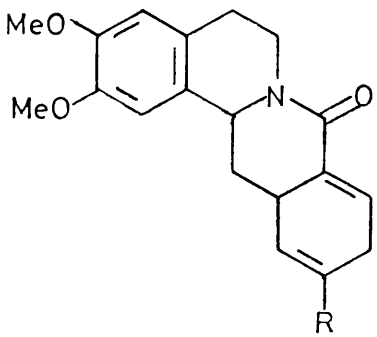
In this case the dienes (128) and (129) are obtained. Hydrolysis of the photocyclised *para*-methoxy analogue [(127), R = OCH_3] affords the ketone (130).



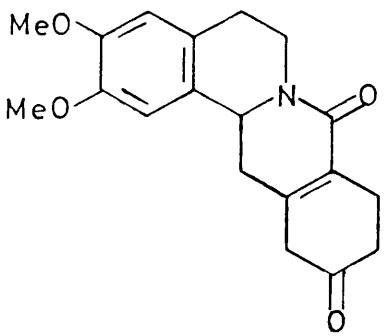
(127)



(128)



(129)



(130)

Although the effects of protic solvents upon the stereochemistry of the final dienamide cyclisation product have been reported, little work has been done with respect to the effect of solvent polarity upon rates of reaction and yields. However, Ogata *et al.*[71] have examined the effect of the dielectric constant of the solvent on the photocyclisation of methacryloylanilide (121) to 3-methyl-3,4-dihydrocarbostyril (122) and have found that the best yields are obtained when the solvents are of very low polarity. For example, the yield of (121) in hexane was 64%, compared to 24% in ether with no cyclisation occurring at all in methanol and acetonitrile after an irradiation time of 8 hours (see Table 2).

Table 2

Photolysis of methacrylanilide in solvents of varying polarity

Solvent	Dielectric constant	Viscosity cP (25° C)	Recovered (121)	Product (122)
CH_3CN	7.5	0.33	89.4	none
CH_3OH	32.6	0.55	96.6	none
$(CH_3)_2CO$	20.7	0.30	80.6	none
i-PrOH	18.3	1.76	96.0	none
n-PrBr	8.1	0.46	60.1	22.3
EtOEt	4.34	0.24	55.5	24.3
C_6H_6	2.28	0.65	53.4	33.0
n-C_6H_{14}	1.09	0.29	17.7	63.5

4.3 Synthetic applications of the dienamide photocyclisation

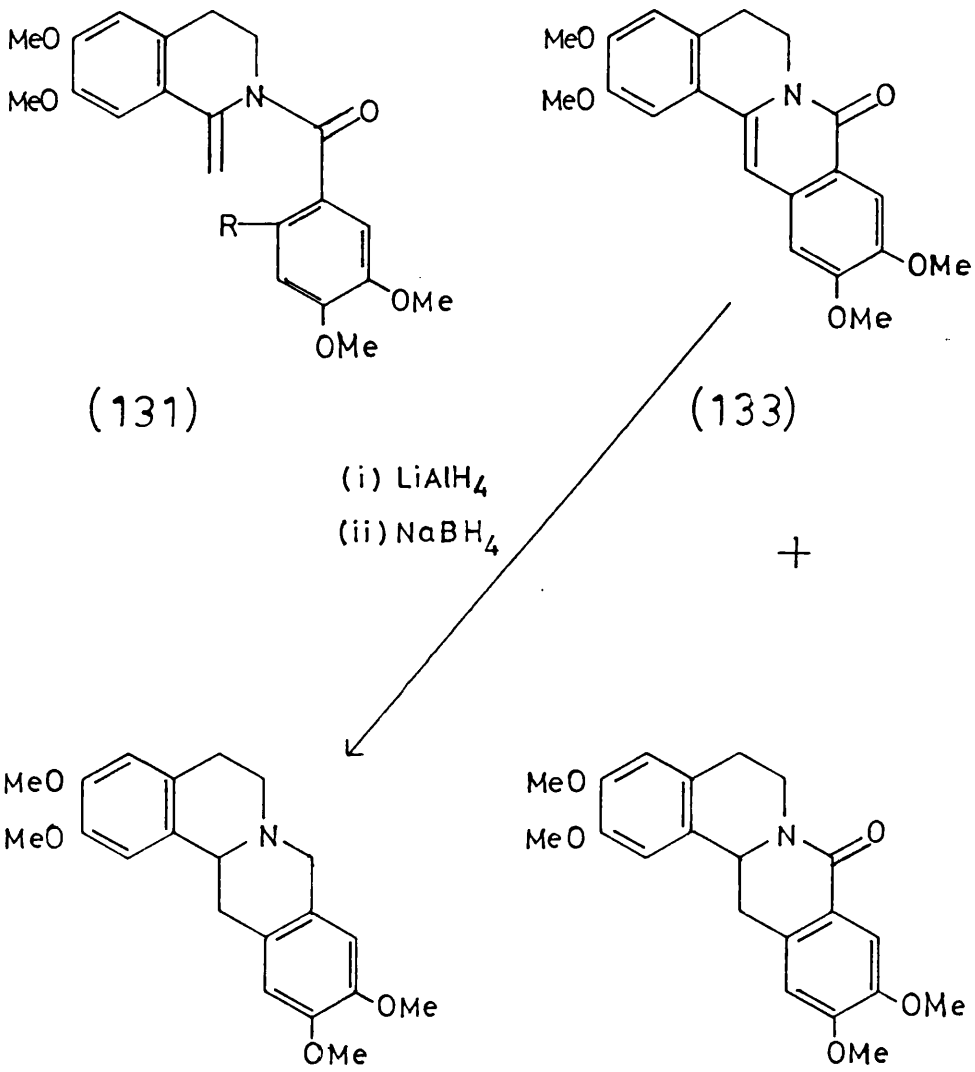
Dienamide photocyclisations have found widespread application in the synthesis of polycyclic heteroaromatics and heterocyclic natural products. A full coverage of the literature regarding these reactions is outside the scope of this chapter and, instead, attention is directed towards the reviews on the subject by Ninomiya[65] and Lenz.[66] However, some of the advantages and disadvantages of the method may be illustrated by reference to two groups of compounds; the protoberberine alkaloids and indole polycycles.

4.3.1 The photochemical synthesis of protoberberine alkaloids

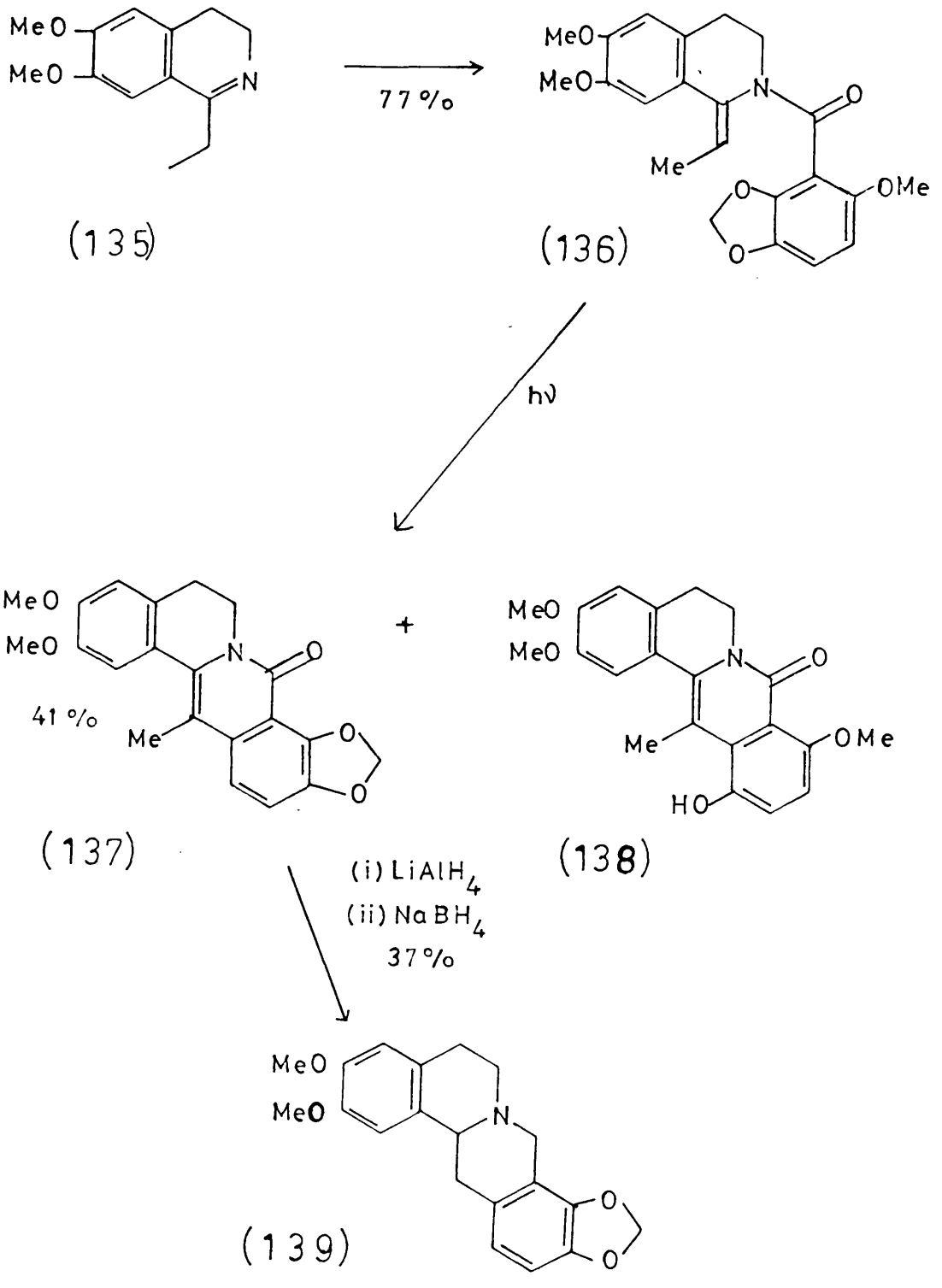
Two approaches have figured prominently in the synthesis of protoberberine alkaloids; early examples of both are represented by the syntheses due to Lenz and Cava described at the beginning of this chapter.

By modifying Cava's approach, Ninomiya[77a] was able to synthesise the alkaloid xylopinine (134), although overall yields were not good (Scheme 30). A similar cyclisation yielded cavidine (139)[81] and hence the formal total synthesis of thalictrifoline was also accomplished (Scheme 31). Again, the overall yields of the target system were poor; a result of the fact that the methylenedioxy moiety exerts a considerable directing influence on the cyclisation so that a significant quantity of a phenolic side product (138) was formed along with the desired product (137). The yield was also further affected by the inefficiency of the subsequent reduction stage.

The problem of low yields in the cyclisation of dienamides such as [(131), R = H] was partially overcome by Kametani[79] through the use of bromine as a directing group. In this way the 8-oxyprotoberberine (133) was obtained in 80% yield by photolysis of the bromodienamide [(131), R = Br]. However, the use of bromodienamides is severely limited by the fact that the directing influence of bromine is weaker than that of the methoxy and methylenedioxy groups. For example, when the 6-bromo-2,3-dimethoxybenzoylenamine (188) was irradiated in benzene, the methoxyl elimination product (189) was formed as the


MeO
MeO
N
O
R
OMe
OMe
(131)
MeO
MeO
N
O
OMe
OMe
(133)
(i) LiAlH4
(ii) NaBH4
+
MeO
MeO
N
OMe
OMe
(134)
MeO
MeO
N
O
OMe
OMe
(132)

Scheme 30


MeO
MeO
N
77 %
(135)
MeO
MeO
N
O
Me
O
O
OMe
(136)
hν
MeO
MeO
N
O
41 %
Me
O
O
(137)
+
MeO
MeO
N
O
Me
OMe
HO
(138)
(i) LiAlH4
(ii) NaBH4
37 %
MeO
MeO
N
O
O
(139)

Scheme 31

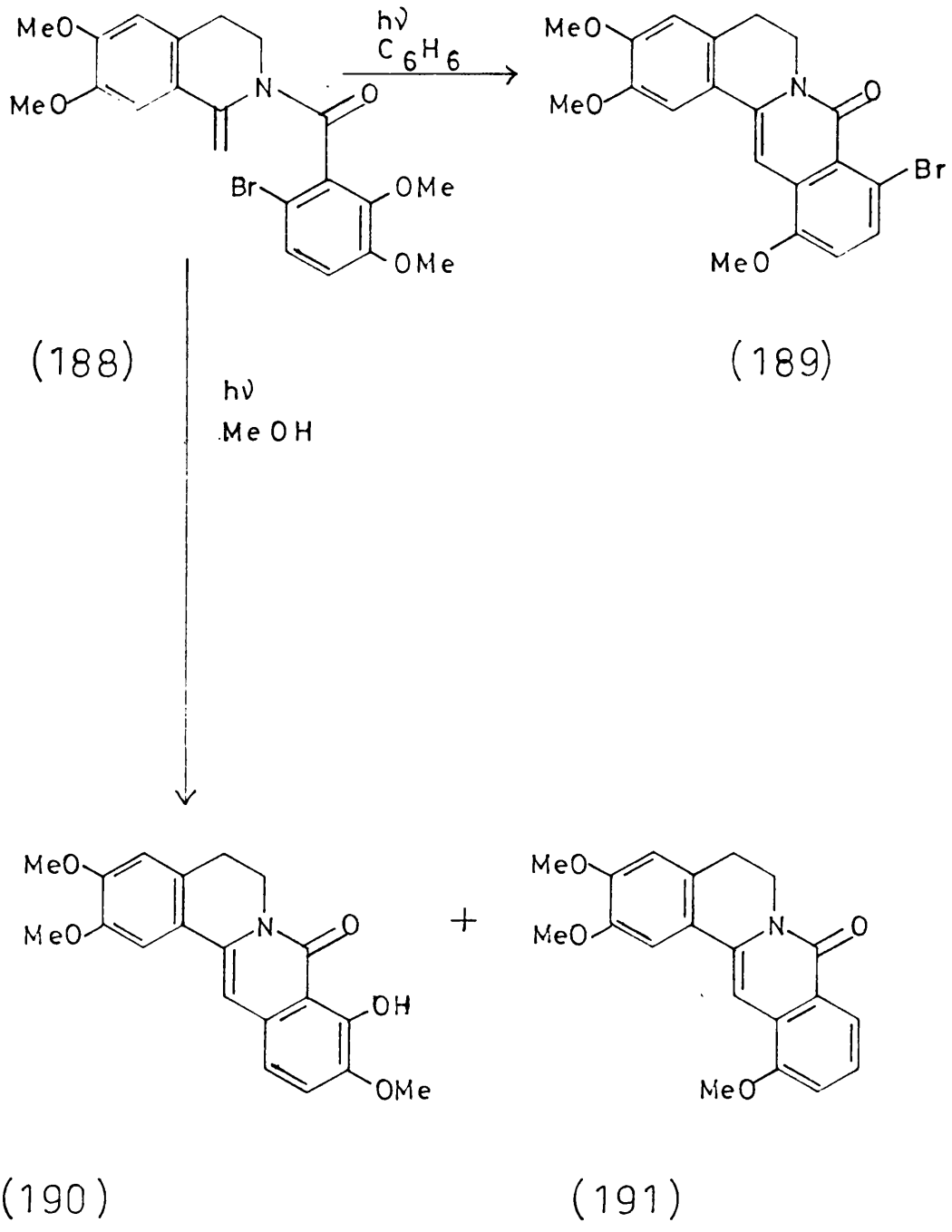
major product (Scheme 32). Interestingly, the reaction appears to be highly solvent dependent since photolysis of the bromodienamide (**188**) in methanol solution afforded two bromine eliminated products; one (**190**) in which cyclisation had occurred at the bromine position and the other (**191**) in which cyclisation had taken place at the root of the methoxy group with subsequent additional elimination of bromine.

The problem of the elimination of alkoxy functions during photocyclisation has been completely overcome by Lenz[85] in his ring closure of formylenamides (141), which may themselves be synthesised by treatment of 3,4-dihydroisoquinolines with mixed acetic-formic anhydride. The irradiation of various methoxy- and methylenedioxy- substituted formylenamides (141) in the presence of hydriodic acid leads to protoberberine iodides (143) in excellent yields with quantitative conversions being achieved in some cases (Scheme 33). This reaction is essentially a cyclodehydration and it is noteworthy that loss of water from the presumed intermediate (142) always takes precedence over loss of methanol or formaldehyde, even when the dienamide *e.g.*, [(64), R_3 = OCH_3 or R_3, R_4 = OCH_2O] is set up for such an elimination.

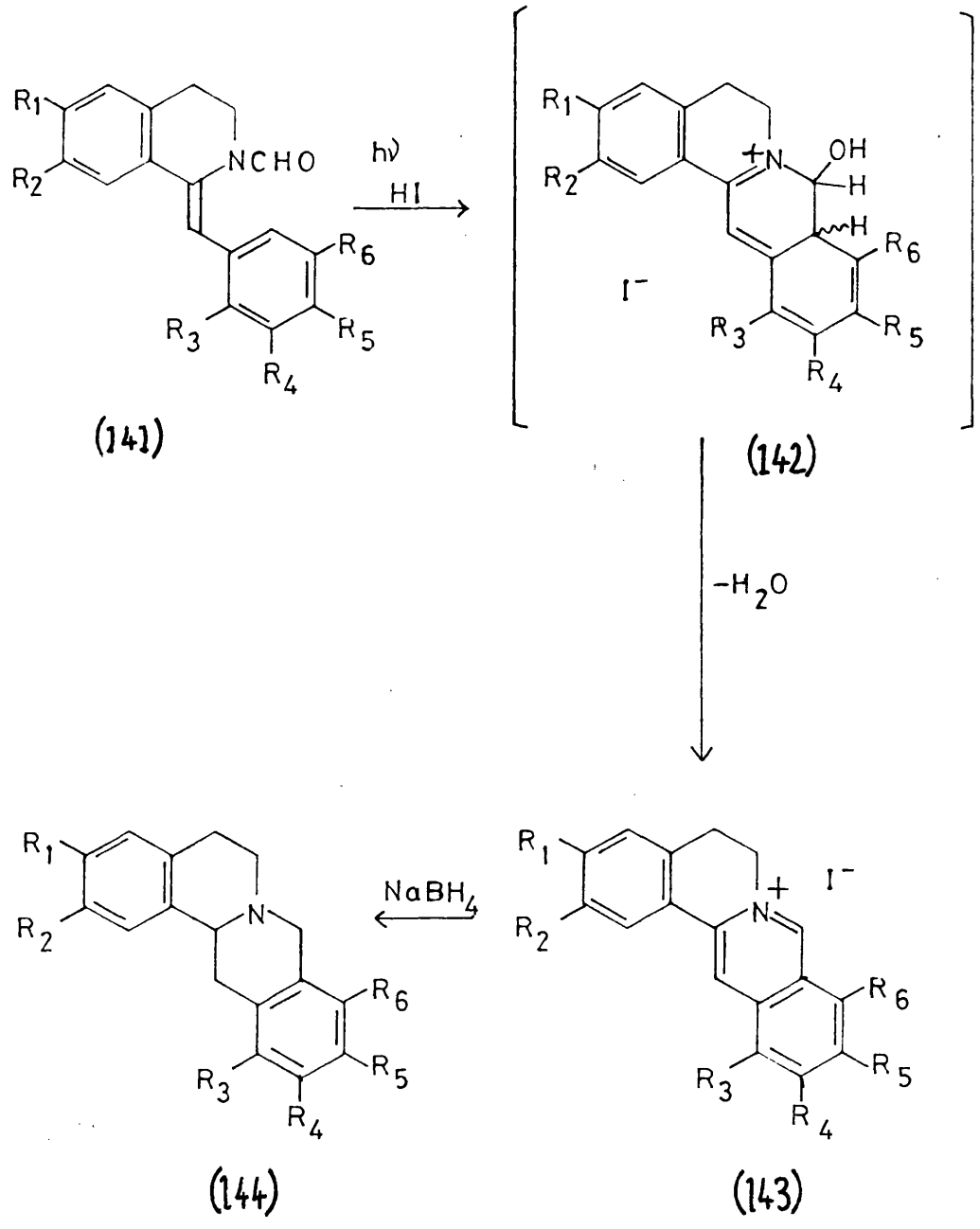
An additional attractive feature of this process is that the protoberberine iodide (143) may be reduced to the tetrahydroderivative (144) with sodium borohydride in very high yield compared with the somewhat cumbersome two step reductions of the 8-oxyprotoberberines (137) reported by Ninomiya.[81]

Good yields of 8-methylberbines (146) have been obtained in a similar fashion by photolysis of the acetyldienamines (145) followed by reduction of the resulting iodide salt with sodium borohydride.[86]

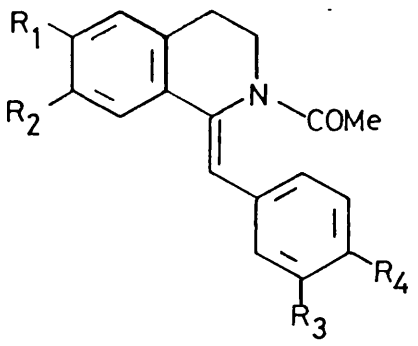
The methods outlined above all lead to racemic mixtures of the protoberberines. Recently, however, several photochemical enantiospecific syntheses of berbines have been reported. Ninomiya[87] has reduced the benzoylenamine [(131), R = H] in the presence of a dilute solution of a lithium aluminium hydride-quinine complex and has obtained optically active (132) and (134) as the products in 10% and 38% yields respectively.



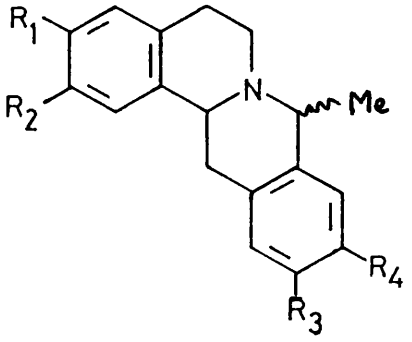
Scheme 32



Scheme 33



(145)



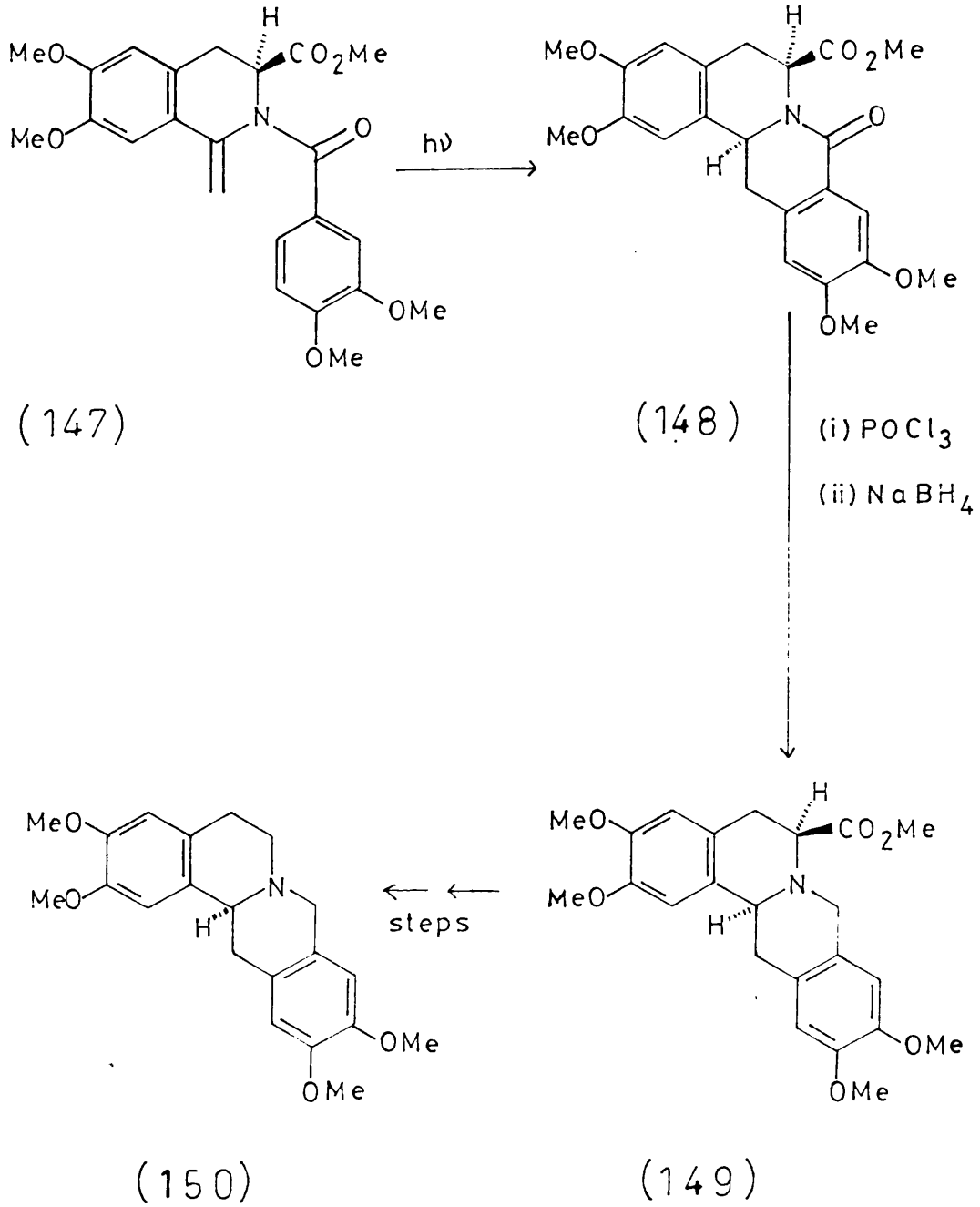
(146)

A different approach, utilising 1,3- asymmetric induction, has been described by Kametani.[88] Exposure to u.v. light of the asymmetric dienamide (147) led to formation of the asymmetric product (148). Reduction of the carbonyl group followed by a decarboxymethylation procedure afforded optically active xylopinine (150) (see Scheme 34).

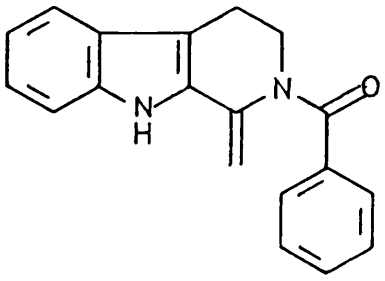
4.3.2 The application of dienamide ring closures to the synthesis of indole polycycles

The aroylation and subsequent photoannelation of Bischler-Napieralski cyclisation products, exemplified by the photochemical syntheses of protoberberines referred to above, has also been used to synthesise indole alkaloids. For example,[89] the oxoyohimbine derivative (152) has been synthesised by benzoylation of harmalan (153) and photocyclisation of the resulting dienamide (151).

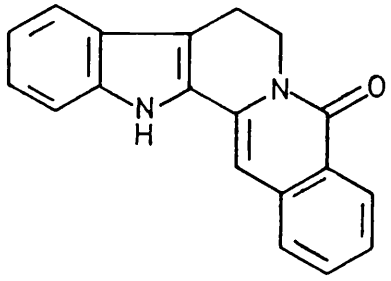
The fully reduced yohimbine skeleton was later prepared by acylation of harmalan with cyclohexenylcarbonyl chloride to give the dienamide (154) which underwent photochemical ring closure to the


MeO
MeO
H
CO2Me
N
O
O
OMe
OMe
hν
(147)
(148)
(i) POCl3
(ii) NaBH4
(149)
steps
(150)

Scheme 34



(151)

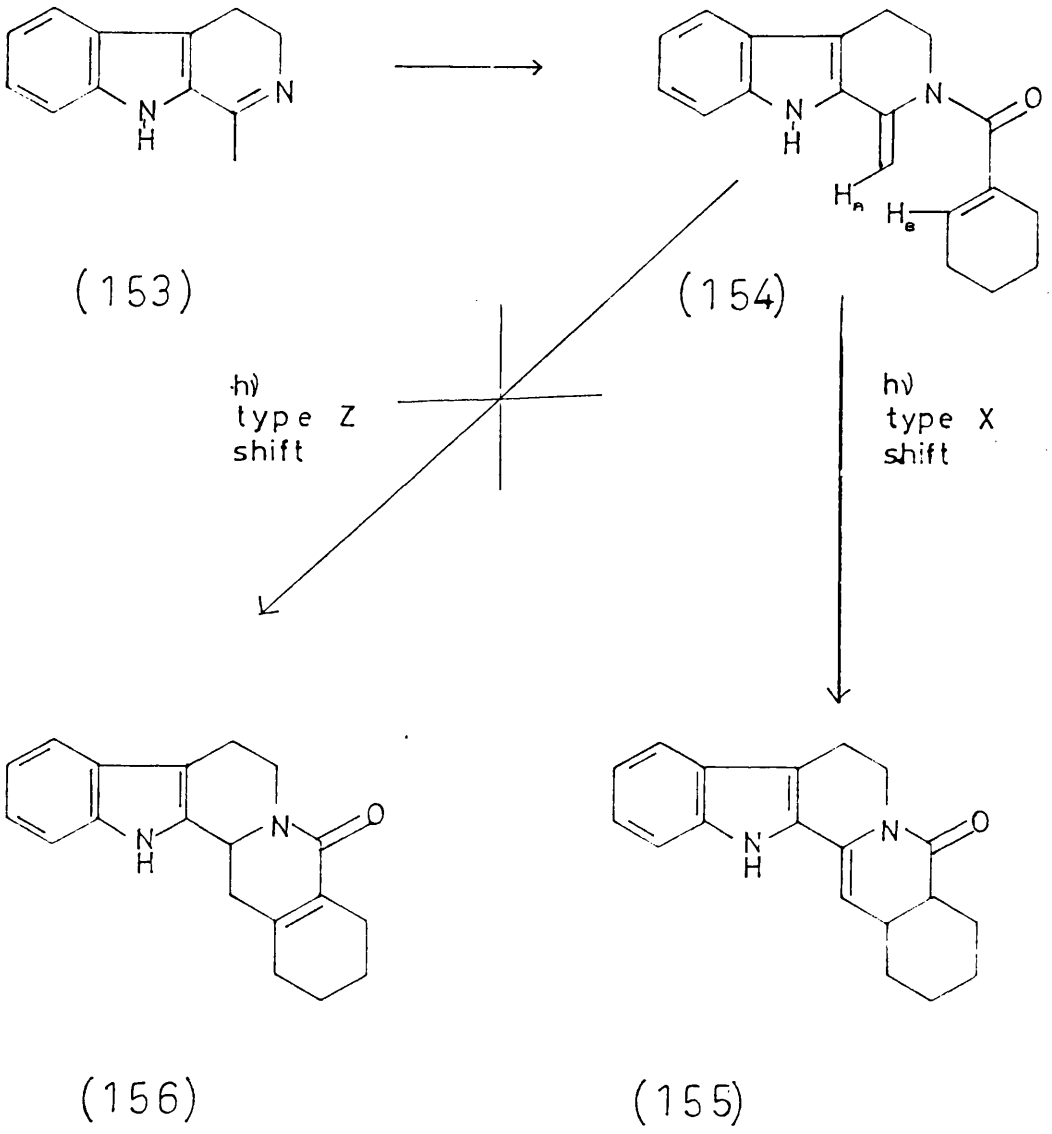


(152)

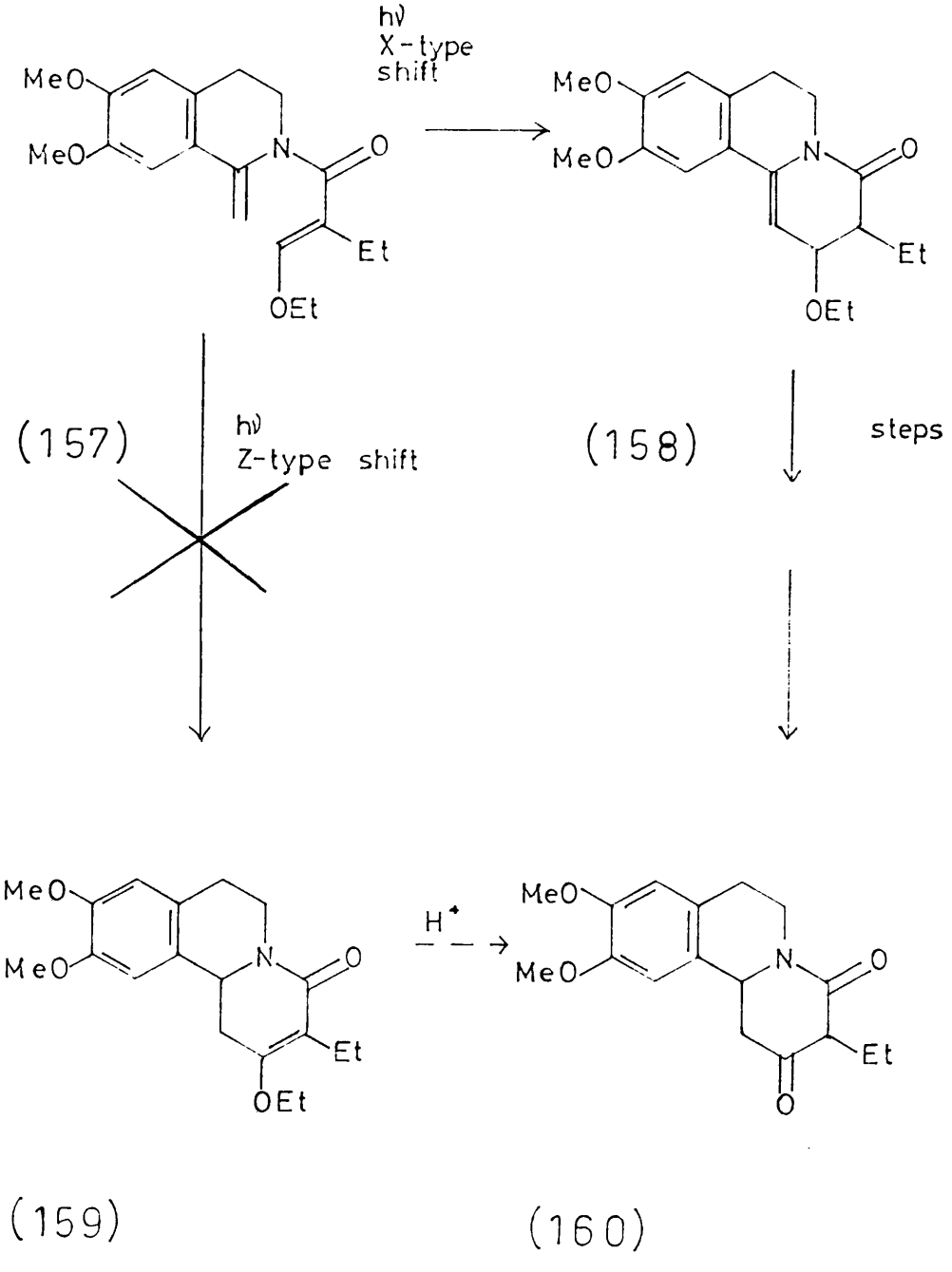
lactam (155).[90] Reduction with LAH and sodium borohydride completed the synthesis. Of great relevance to the work contained in the following chapter is the fact that whilst both type X (migration of H_A) and type Z (migration of H_B) sigmatropic shifts are theoretically possible with this molecule, the type X shift occurs exclusively to regenerate the enamine configuration, rather than the α,β-unsaturated carbonyl function. (Scheme 35).

During a related synthesis, in which a precursor of the isoquinoline alkaloid emetine was the objective, the preference for a type X migration was also observed. This result was clearly disappointing because, if cyclisation of the ethoxydienamide (157) had been followed by a type Z shift, simple hydrolysis of the enol-ether linkage in the product (159) would have afforded the emetine precursor (160). Instead, both reduction and oxidation steps were required to transform the actual cyclisation product into the desired product (see Scheme 36).

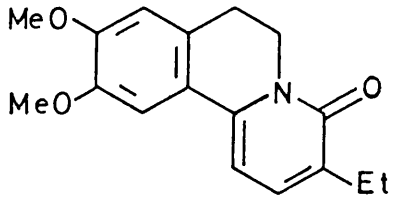
Attempts to hydrolyse the lactam (158) with acid resulted in formation of the fully aromatised species (161) through elimination of ethanol.



Scheme 35

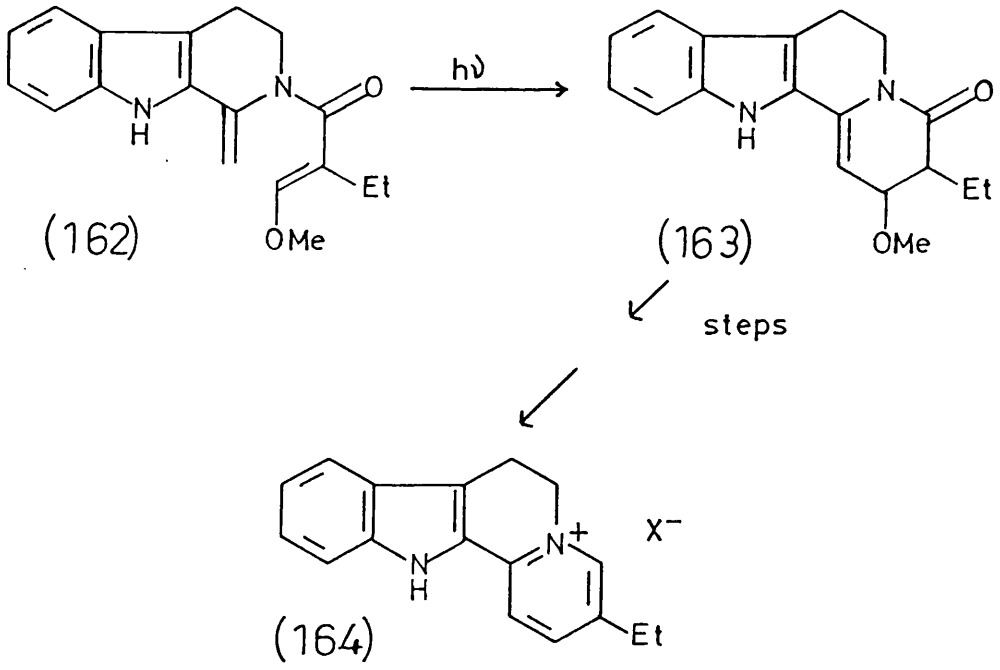

hν
X-type
shift
MeO
MeO
N
O
Et
OEt
(157)
hν
Z-type shift
(158)
steps
H+
(159)
(160)

Scheme 36



(161)

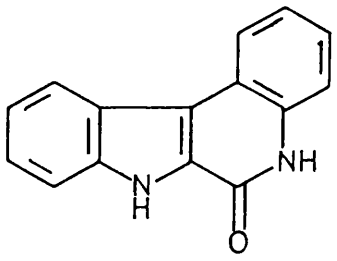
This type of elimination was used as a key feature in the synthesis[90] of flavopereirine (164) *via* photocyclisation of the methoxydienamide (162) (see Scheme 37).



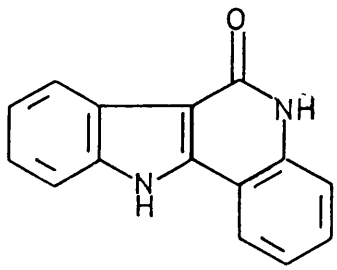
Scheme 37

Dienamide cyclisations have also been used to prepare members of the "azayohimbine" class of alkaloids. Acylation of harmalan (153) with a variety of appropriately substituted nicotinoyl chlorides affords dienamides which can be photocyclised to yield a number of compounds that have been found to occur naturally in such plants as *Strychnos angustiflora* Benth and *Nauclea parva* Merrill (see Scheme 38).[89,92-94] Both Ninomiya *et al.*[89,92] and Sainsbury[93] have found that the photocyclisation of nicotinoylenamine (165) is non-regiospecific with ring closure occurring to both the 2- and 4- positions of the pyridine ring; for example, irradiation of the unsubstituted dienamide [(165), R_1, R_2 and R_3 = H] results in the formation of both naucléfine [(166), R_1, R_2 and R_3 = H] and isonaucléfine [(167), R_1, R_2 and R_3 = H]. However, by treating the dienamide [(165), R_1, R_2 and R_3 = H] with benzyl bromide, a regiospecific ring closure is induced to give exclusively the naucléfine benzyl bromide salt.[94] Debenzylation is achieved readily to yield the parent alkaloid [(166), R_1, R_2 and R_3 = H]. The regiospecificity of this chemical cyclisation is thought to be a result of the steric effect of the bulky benzyl group inhibiting ring closure to the pyridine 2- position.

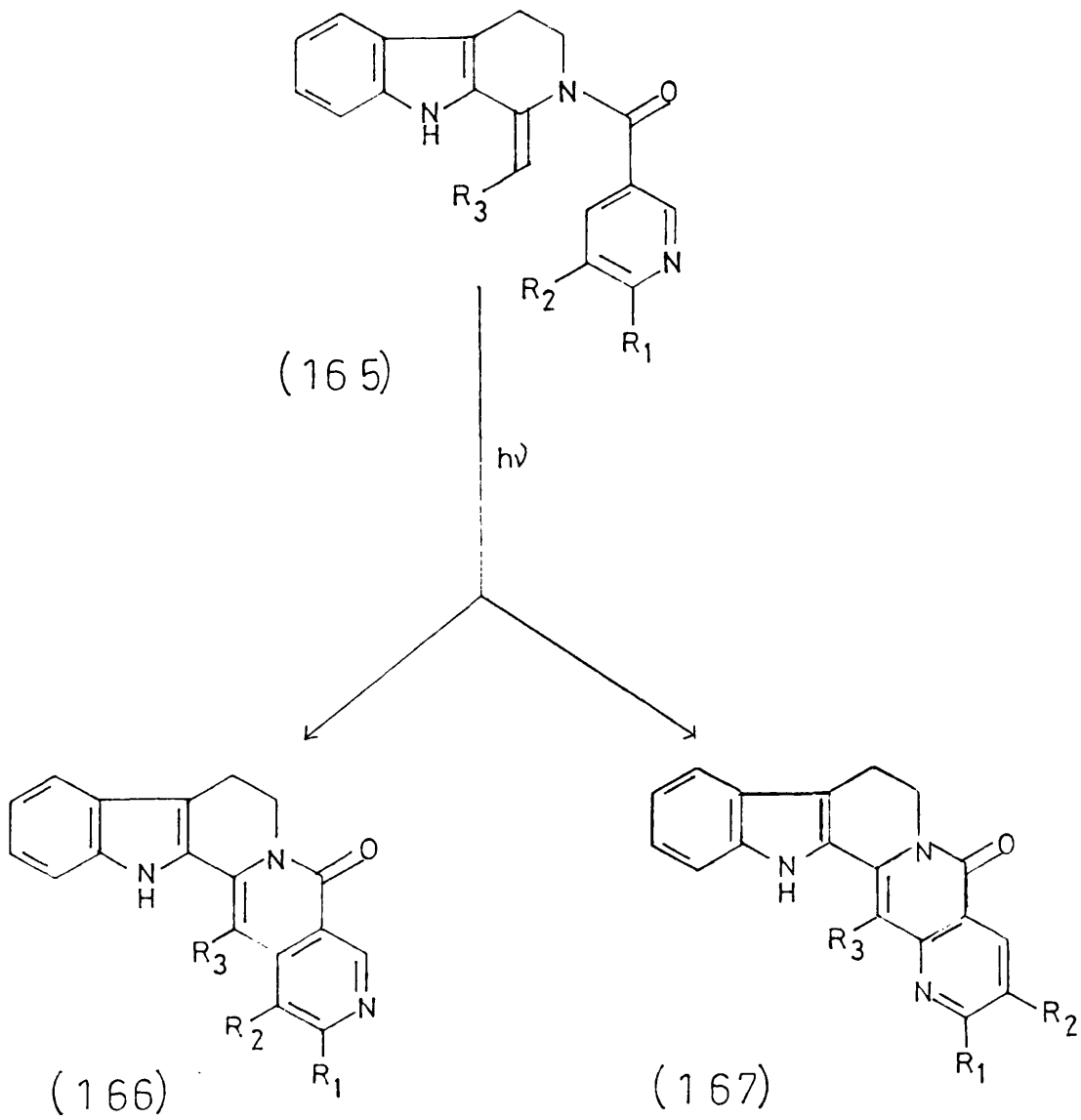
Early examples of the application of dienamide photocyclisation to the preparation of indole polycycles are Winterfeldt's syntheses[95] of the benzo-fused β- and γ-carbolines (168) and (169) by cyclisation



(168)



(169)

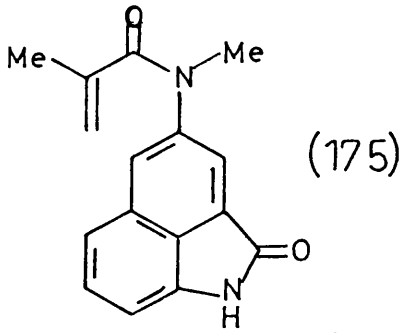


Scheme 38

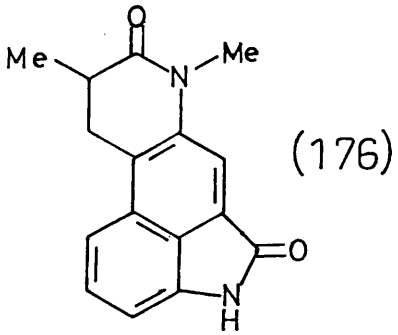
of the anilides of indole-2- and -3-carboxylic acids. Although the yields quoted by Winterfeldt were low, Kanaoka[96] was subsequently able to reinvestigate the reaction and obtain yields in excess of 70%. These syntheses beautifully illustrate the true value of the dienamide method in that simple, easily obtained, starting materials may be coupled together and cyclised in good yield to polycyclic compounds which are often difficult to make by more conventional means.

In contrast, Ninomiya's attempt[97] to synthesise the clavines (174) *via* a dienamide photoannelation (Scheme 39) utilised a "starting material" (170) which has been the object of considerable synthetic endeavour itself.[98] In the event, cyclisation of the dienamide (172) could not be induced photochemically, although moderate yields of the ring closed product (173) were obtained through thermal cyclisation. Two further reductions and an oxidation were required before a low yield of a stereoisomeric mixture of the clavines was obtained.

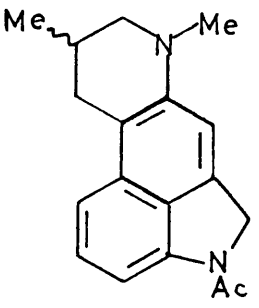
Greater success was achieved with an aromatic analogue (177) of the clavines which was synthesised by photocyclisation of the acyl-β-naphthylamine derivative (175) followed by reduction and acetylation of the resulting lactam (176).[99] However, adjustment of the oxidation state of the product (177) to give the clavines (174) is not a trivial process and hence the usefulness of this procedure is limited.



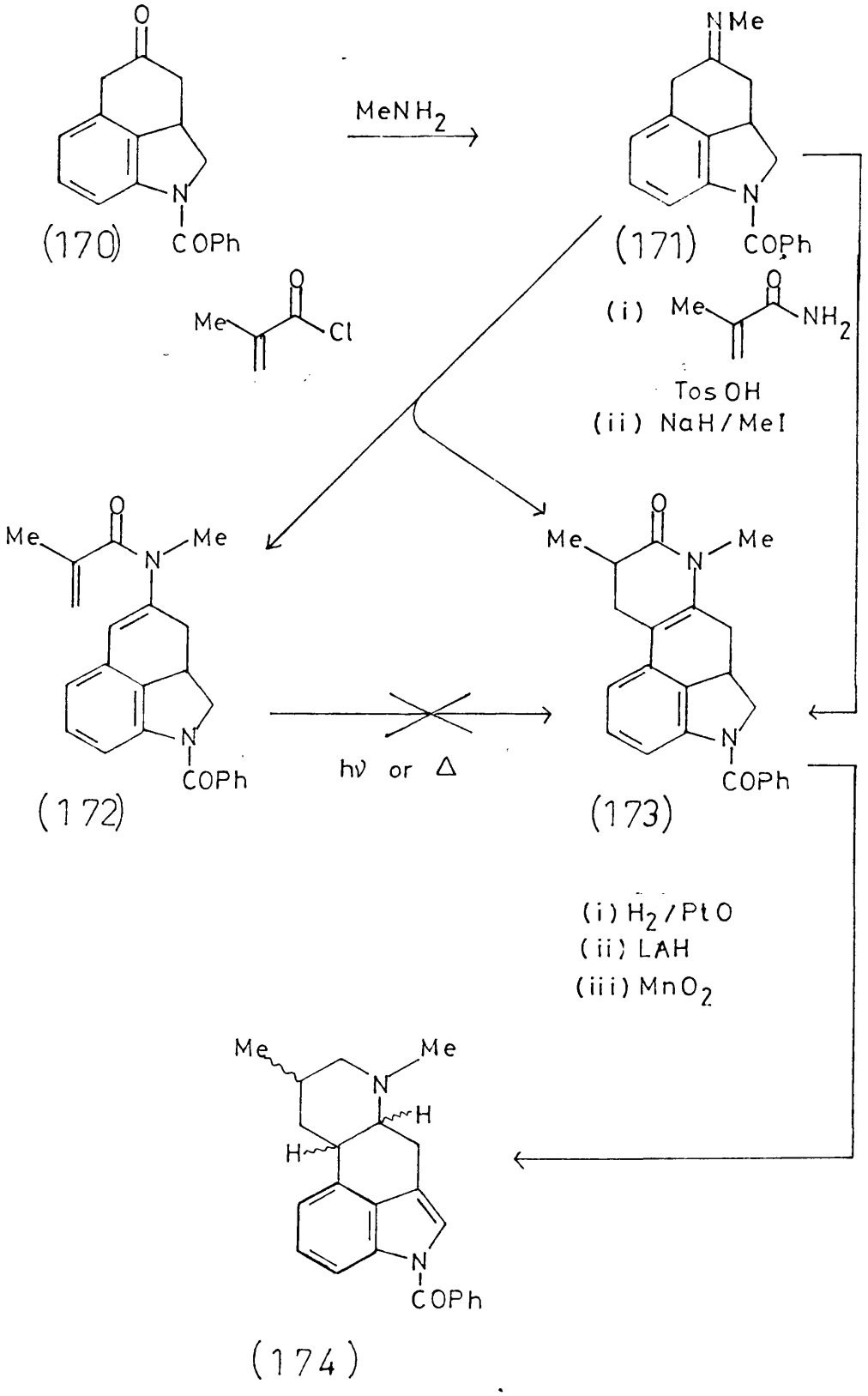
(175)



(176)



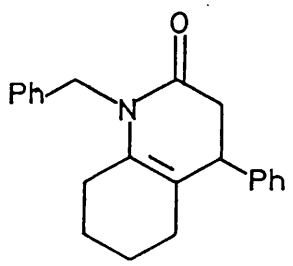
(177)


MeNH2
(170)
COPh
(171)
(i) Me NH2
Tos OH
(ii) NaH/MeI
Me Cl
(172)
hν or Δ
(173)
(i) H2/PtO
(ii) LAH
(iii) MnO2
(174)

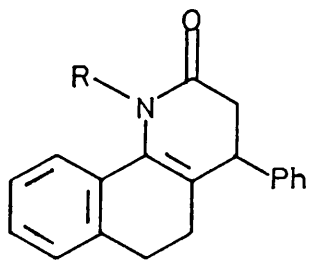
Scheme 39

4.4 Thermal reactions of dienamides

Finally, brief mention should be made of the thermally induced cyclisations of dienamides. Whereas the photochemical cyclisations of this class of compounds have been widely studied, the literature coverage of the thermal equivalent has been sparse. It may be that this is due to the dienamides lacking ground state reactivity, although several cases are known in which the reactivity of the dienamide has been such that it has proved unisolable. For example, acylation of the *N*-benzylimine of cyclohexanone with cinnamoyl chloride results in the formation of the hexahydrocarbostyril (178).[100] The presumed dienamide intermediate could not be isolated. Similarly, treatment of the imine of α-tetralone with cinnamoyl chloride brought about spontaneous cyclisation to the tetrahydrophenanthridone (179).

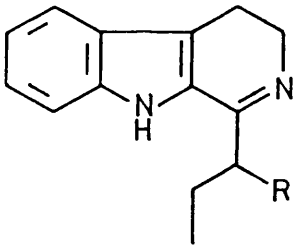


(178)

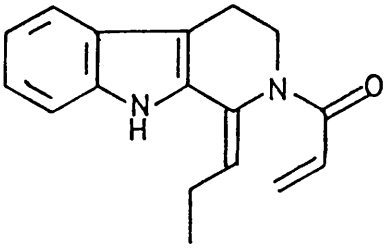


(179)

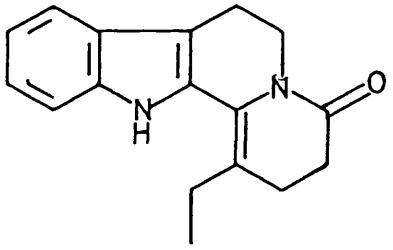
Reaction of the 3,4-dihydro-β-carboline [(180), R = H] with acrylic acid in boiling xylene leads to a high yield of the indoloquinolizine (182), presumably *via* the intermediate dienamide (181).[101] In this case, evidence for the intermediacy of the dienamide was obtained when it was formed as the sole isolable product upon acylation of the imine [(180), R = H] with acrylic acid/diphenylphosphorylazide or acryloyl chloride. A spontaneous cyclisation of a substituted



(180)



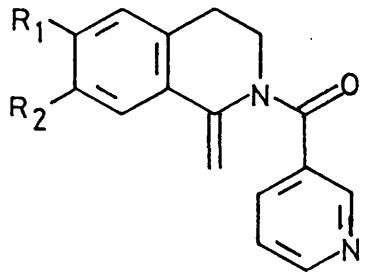
(181)



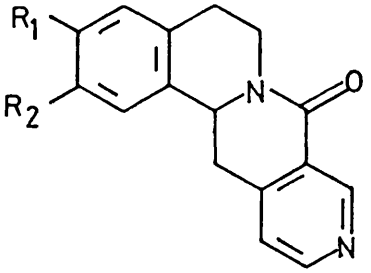
(182)

acryloylenamine leading to a clavine precursor has already been described (see Scheme 39).

Several modes of thermal cyclisation are possible. For instance, the thermal ring closure of the nicotinoylenamine (183) to the pyridoquinolizine derivative (184)[102] is probably a concerted reaction in the



(183)



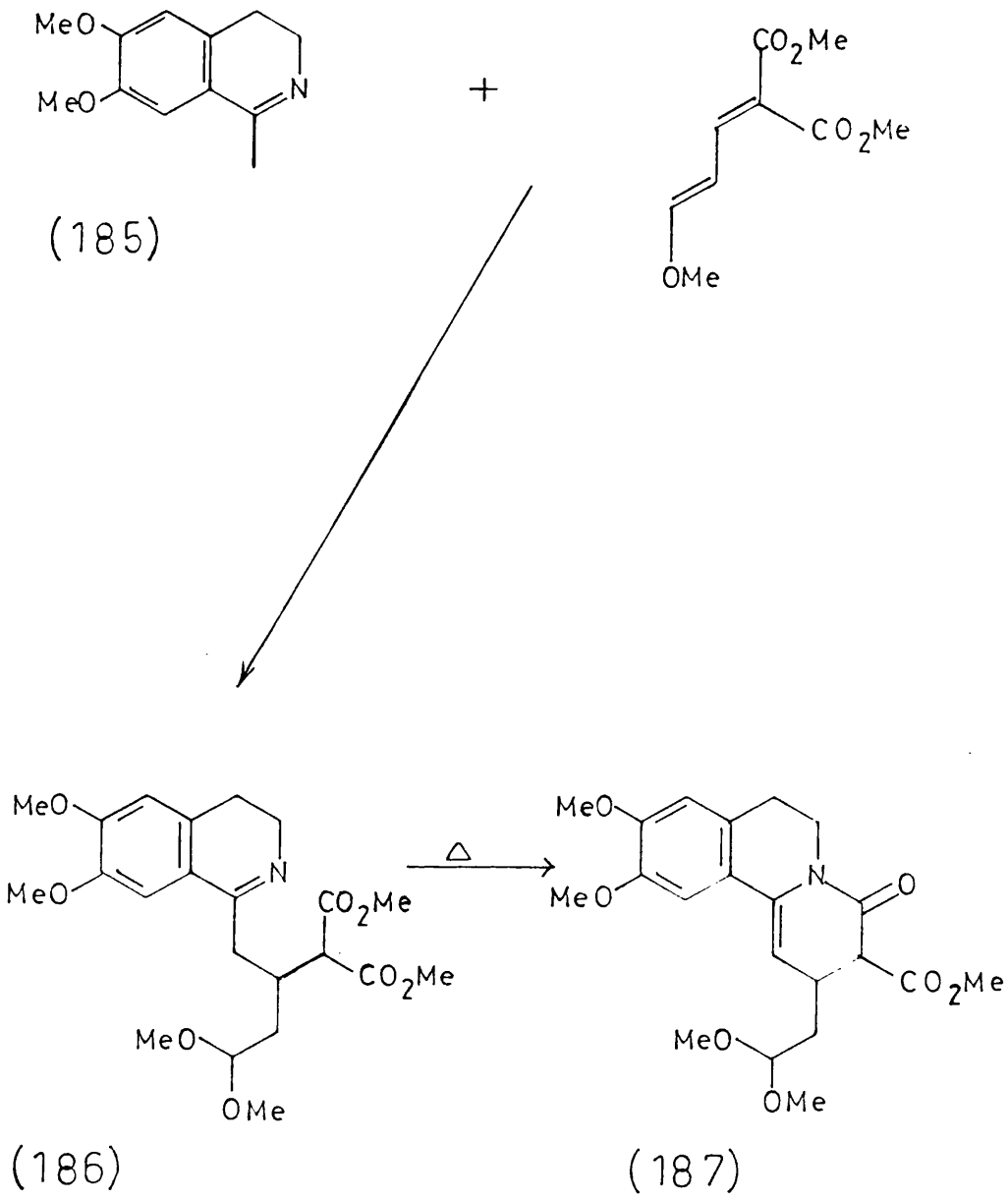
(184)

Woodward-Hoffmann sense.[73] However, a second type of ring closure can be envisaged in which initial Michael addition of an enamine to an α,β-unsaturated carbonyl unit is followed by the enamine nitrogen attacking the carbonyl function to complete the cyclisation. The enamine character of imines such as harmalan (153) is well known.[103]

An example of this type of ring closure is the reaction of the β-carboline imine [(180), R = H] with methylacrylate to give the ester [(180), R = $CH_2CH_2CO_2Me$] with further heating resulting in cyclisation to the indoloquinolizine (182).

A Michael adduct (186) was also detected as an intermediate in the formation of the benzoquinolizine (187) by reaction of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (185) with dimethyl-3-methoxyallylidene-malonate (Scheme 40).[104]

This "enamine annellation" technique has subsequently been extended to cover the synthesis of a number of β-carboline alkaloids of the corynantheine family.[105]


MeO
MeO
N
(185)
+
CO2Me
CO2Me
OMe
MeO
MeO
N
CO2Me
CO2Me
MeO
OMe
(186)
Δ
MeO
MeO
N
O
CO2Me
MeO
OMe
(187)

Scheme 40

CHAPTER 5

5.1 The synthesis of indolo[2,3,-*c*]isoquinolines

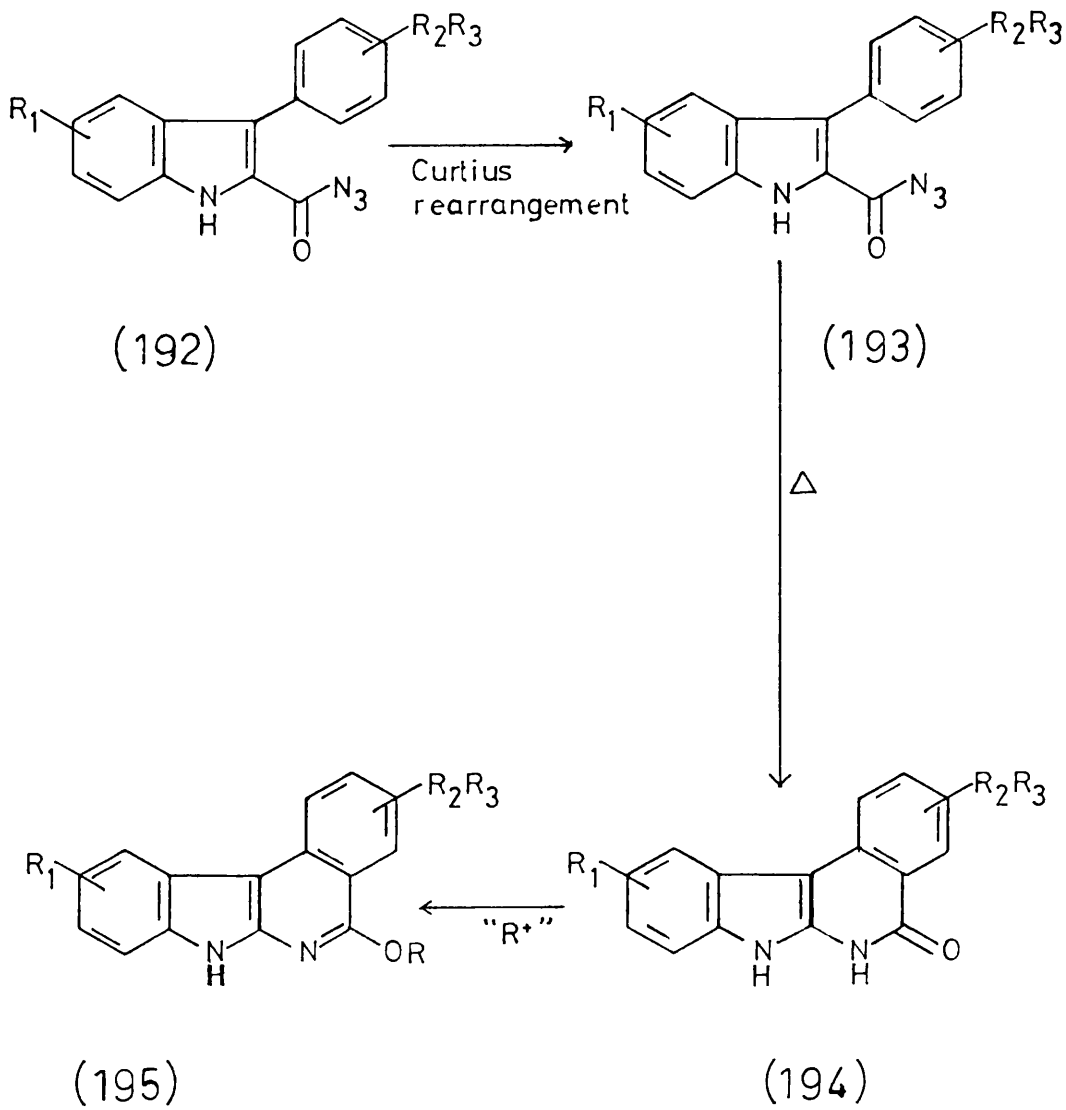
A considerable amount of effort at Bath[46] has been devoted to the synthesis of compounds which show anti-cancer activity, particularly those, such as the ellipticines, which act by intercalating between the base pairs of the DNA molecules.

Recently,[106] a synthesis of indolo[2,3,-*c*]isoquinolines (195) has been reported along with the observation that such compounds are potent anti-cancer agents. The planar arc shape of these molecules makes it likely that they too are intercalating drugs.

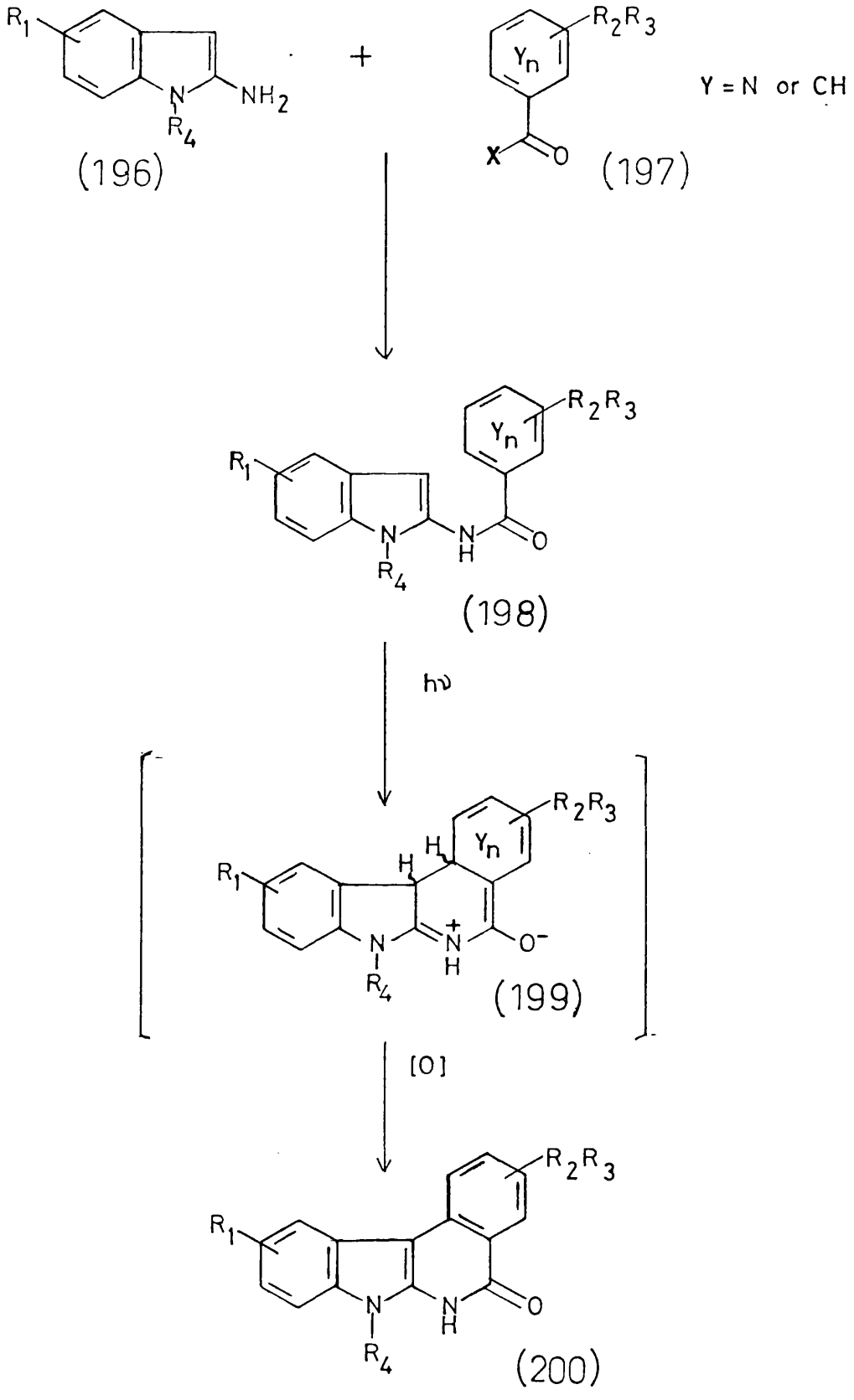
The reported synthesis (Scheme 41) is a development of an earlier route[107] and involves Curtius rearrangement of the azide (192) to the intermediate isocyanate (193), followed by thermal cyclisation to the indoloisoquinolone (194). This product is then alkylated to give the target system (195). Analysis of the structure (194) led us to the conclusion that a simple and versatile alternative synthesis could involve aroylation of 2-aminoindoles followed by photocyclisation of theresulting dienamide (Scheme 42).

Such a scheme would permit the incorporation of various hetero-atoms into the D-ring of the parent structure.

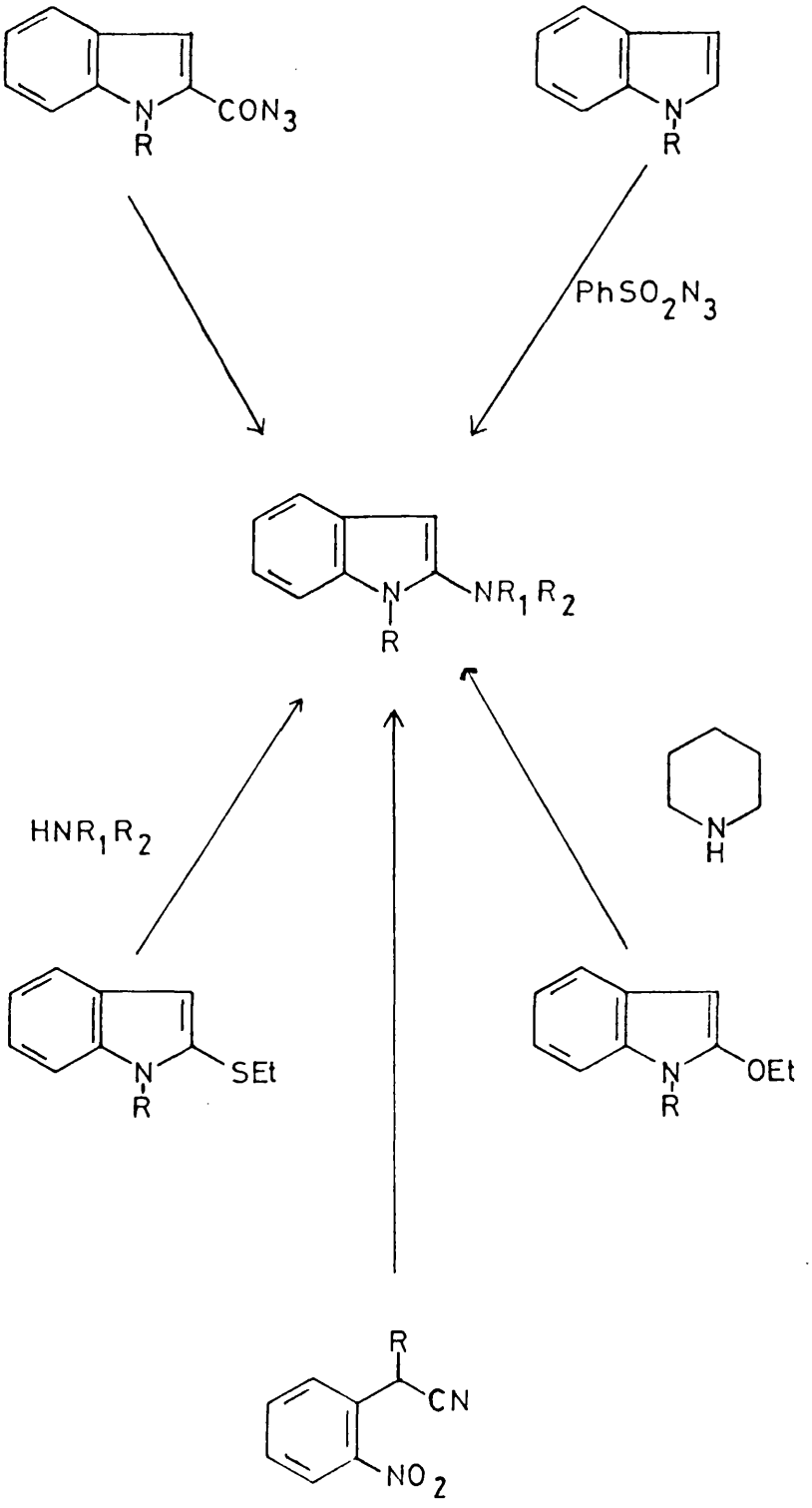
Aminoindoles have previously been synthesised in a number of ways,[108] the most important of which are described in Scheme 43. However, the literature description of 2-aminoindoles highlighted several problems which would have to be overcome in any successful synthesis. The first of these is their extreme sensitivity towards aerial oxidation. This is undoubtedly a result of the high electron density at the β-position, caused by the cross conjugated double enamine system, which permits peroxide formation to take place. Such peroxides and their decomposition products have been isolated and characterised [equation (23)].[109]



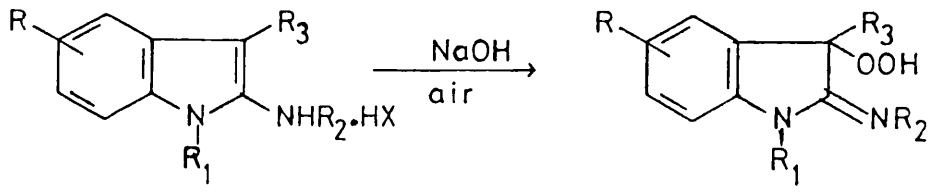
Scheme 41



Scheme 42 Projected route



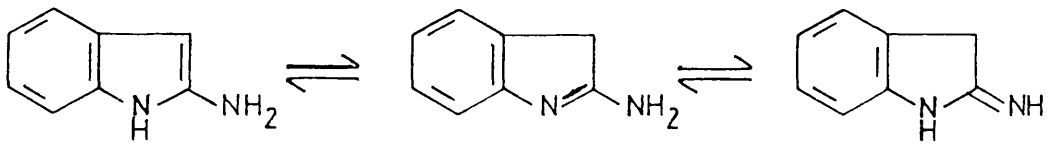
Scheme 43 Synthesis of Aminoindoles



(23)

Routine handling of the aminoindoles under an inert atmosphere would minimise oxidation, but the m ajor problem we anticipated concerns the necessity for utilising oxidising conditions during the photochemical reaction in order to bring about conversion of the dihydro intermediate (199) to the desired aromatic system (200), even though an amide unit now replaces the exocyclic amino function.

The other complication is the fact that 2-aminoindoles can exist in three tautomeric forms [equation (24)]. Which tautomer predominates depends to a large extent on the substituents.



(24)

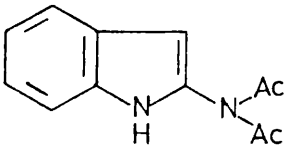
(201) (202) (203)

Kebrle and Hofmann[108b] have examined the u.v. spectra of various 2-aminoindoles and have concluded that 1-unsubstituted aminoindoles prefer to exist in the 3H-indole (indolenine) form. This was confirmed

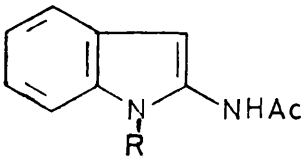
by ^{1}H n.m.r. studies of Witkop and Hino[110] in which no resonances due to a β-hydrogen or the N-H function were observed. Hino *et al.* also concluded that 1-substituted-2-aminoindoles exist as a tautomeric mixture of 1H-indole and iminoindoline (203) structures.

One result of the tautomerism is that *N*-substitution reactions, such as acylation, tend to show poor regiospecificity. This problem is illustrated nicely by the acetylation reactions of 2-aminoindole.

The acetylation of 2-aminoindole was originally investigated by Pschorr and Hoppe[108a] who found that treatment with excess acetic anhydride gave rise to a diacetyl compound which they did not identify. No yield was quoted for this procedure and so it is unclear whether any other acetylation products are formed in the reaction. Rinderknecht[108c] suggested that Pschorr's diacetyl compound had the *N'*-disubstituted structure (204), but Kebrle and Hofmann[108b] subsequently used Pschorr's acetylation conditions with 1-methyl-2-aminoindole to give only the monoacetyl derivative, thereby indicating that Rinderknecht's assignment was incorrect and that the correct structure was, in fact (205), (R = $COCH_3$).



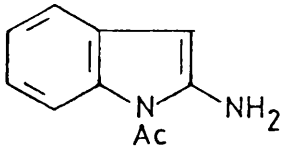
(204)



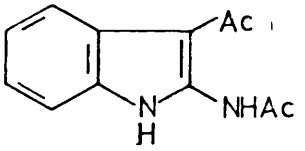
(205)

A different result was obtained when 2-aminoindole was treated with slightly less than one equivalent of acetyl chloride in pyridine. The major product, for which no yield was quoted, was 1-acetyl-2-aminoindole (206). After successive recrystallisations of the neutral

fraction, a significant (∿10%) yield of 2-acetamido-3-acetylindole (207) was also obtained.[108b] It was demonstrated that this latter



(206)



(207)

product could arise through further acetylation of 2-acetamidoindole [(205), R = H], although when [(205), R = H] was treated with excess acetic anhydride at reflux, some 1-acetyl-2-acetamidoindole [(205), R = $COCH_3$] was formed in addition to the desired compound.

It is thus evident that the 1-, *N*- and 3- positions of 2-aminoindole are of comparable reactivity and that under the conditions used for acylation, more than one acylation product may frequently be obtained.

It seemed to us that the problem of the unpredictable regiochemistry of 2-aminoindole could be avoided by introducing the amino function directly into a preformed *N*-protected indole nucleus. This could, in principle, be achieved by treatment of a 2-lithiated-*N*-protected indole with a suitable aminating agent.

The 2-lithiation of indoles has been carried out in compounds bearing a range of *N*-substituents as diverse as $-CH_3$,[111] $-CH_2OCH_3$,[112] $-SO_2Ph$[113] and $-CO_2CH_2Ph$.[114] Two effects operate to stabilise the lithiated species. The first of these is the negative inductive effect of the nitrogen atom and the second is the presence, in the *N*-substituent, of a heteroatom which may co-ordinate with the lithium.

2-Lithio-*N*-methylindole does not utilise heteroatom co-ordinative stabilisation and as a result is less readily formed and more reactive than, for example, the *N*-phenylsulphonyl analogue.

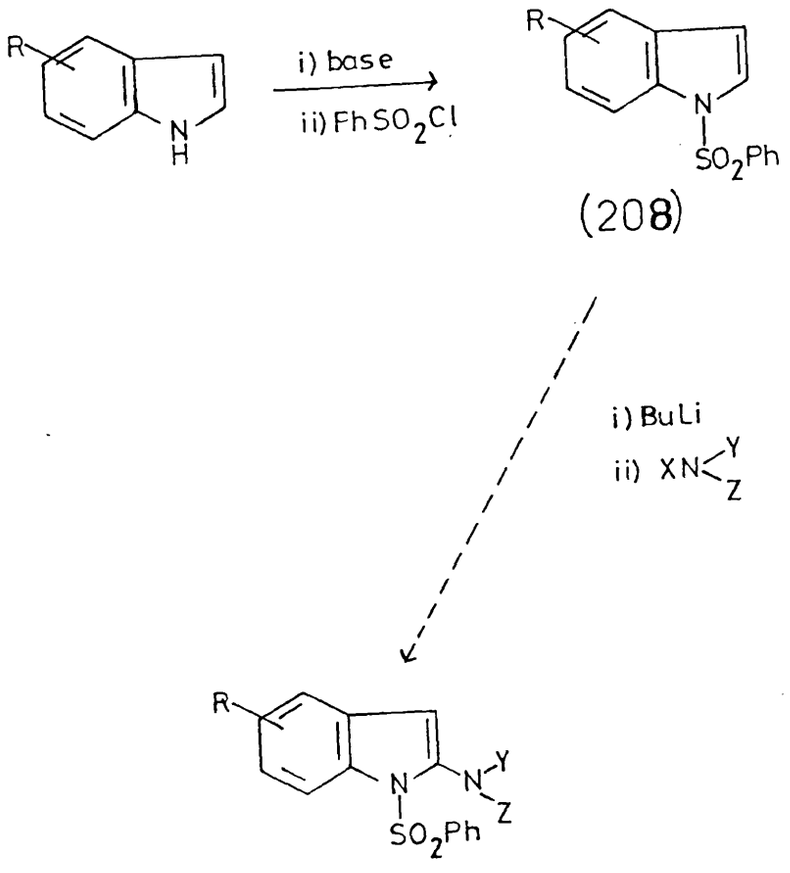
In addition to its ability to facilitate the lithiation process, we required the protecting group to possess two other important properties. Firstly, it should be easily removed under mild conditions and secondly, it should exert a net electron withdrawing effect on the ring which would help to reduce the ease of oxidation of the subsequently formed 2-aminoindole as well as deactivating the 3-position towards substitution during the aroylation reaction. The group fulfilling all these criteria is the phenylsulphonyl group and thus the projected route to 2-aminoindoles was as shown below (Scheme 44).

5.2 The reaction of 2-lithio-1-phenylsulphonylindole with electrophiles

N-Phenylsulphonylindole [(208), R = H] was prepared by reaction of indole with either potassium hydroxide or sodium hydride in DMSO to give the indole anion, followed by treatment with benzenesulphonyl chloride. Work up and recrystallisation gave yields of the order of 70%.

Lithiation was achieved readily by addition of one equivalent of *n*-butyl-lithium to a cold solution of *N*-phenylsulphonylindole in THF. In order to ascertain whether metallation had accurred, the reaction mixture was quenched with deuterium oxide. Subsequent ^{1}H n.m.r. analysis of the product showed that deuterium incorporation had taken place. This was evident from the fact that the resonance due to the β-hydrogen appeared as a singlet rather than the usual doublet. Quenching the lithiation reaction mixture with crushed dry ice resulted in a good yield of *N*-phenylsulphonylindole-2-carboxylic acid, so providing further proof that metallation was taking place.

Having satisfied ourselves in this respect, the 2-lithiated indole was treated with the aminating agent mesitylenesulphonylhydroxylamine (MSH), but the first attempt resulted only in the return of the starting material. This we attributed to the wetness of the reagent as prepared by Tamura's method[12b] (see Chapter 2), but after drying[26]


R
N
H
i) base
ii) $PhSO_2Cl$
R
N
SO_2Ph
(208)
i) BuLi
ii) $XN<^{Y}_{Z}$
R
N
N
Y
Z
SO_2Ph
(209)

Scheme 44

a solution of MSH over 4 Å molecular sieves, and addition of the dried reagent to the lithiated indole, *N*-phenylsulphonylindole was still returned. T.l.c. analysis showed that the MSH had been consumed during the reaction, but no 2-aminoindole was identified. Finally, MSH was prepared by the method of Johnson,[48] whereby a drier, more crystalline, product is obtained. Addition of this reagent did not result in amination, but this time a vigorous reaction ensued with the evolution of a large volume of gas taking place.

It therefore appears that although successful *C*-aminations have been reported,[23,24,26] in our case base catalysed decomposition of the reagent was taking place. This phenomenon, which is discussed at length in Chapter 1, is demonstrated by all the hydroxylamine or haloamine based aminating agents although, in the case of the hydroxylamines, the mechanism may vary, according to the nature of the substituents. In view of this and in the absence at that time of any other suitable aminating agents, we decided to turn our attention to the use of amine precursors *e.g.*, nitro- or nitroso- groups in the hope that this would provide a facile route to aminoindoles.

The solid nitrating agent nitronium tetrafluoroborate was thus added to the lithiated indole at -78° C, but after slow warming to room temperature overnight, no products were observed, although the solution had acquired a pale-straw colour. Similarly, the addition of nitrosonium tetrafluoroborate failed to give 2-nitroso- -phenylsulphonylindole. The failure of these reactions became a little more understandable when it was found that the reagents are unstable in THF. At room temperature, vigorous evolution of gas took place and in the case of the nitronium salt, the straw colour of the resulting solution is indicative of dinitrogen tetroxide formation. Both reagents also proved to be unstable in other solvents (*e.g.*, HMPT, ether, DMF) commonly used to stabilise carbanions. Attempts to lithiate *N*-phenylsulphonylindole in dichloromethane solution predictably failed.

Isoamylnitrite has been used for *N*-nitrosations[115] and so, armed with this precedent, we attempted to extend its use to *C*-nitrosations. However, addition of this reagent to the 2-lithioindole gave results of a type by now familiar to us; thus starting material was recovered whilst the reagent underwent decomposition.

Friedman[115] has reported the base catalysed decomposition of isoamylnitrite and has proposed the following mechanism (Scheme 45) based upon the fact that addition of hot sodium amyloxide to isoamylnitrite results in a near quantitative yield of nitrous oxide.

$$RCH_2ONO + B^- \longrightarrow R\bar{C}H\text{-}ONO + BH$$

$$R\bar{C}HONO \longrightarrow RCHO + NO^-$$

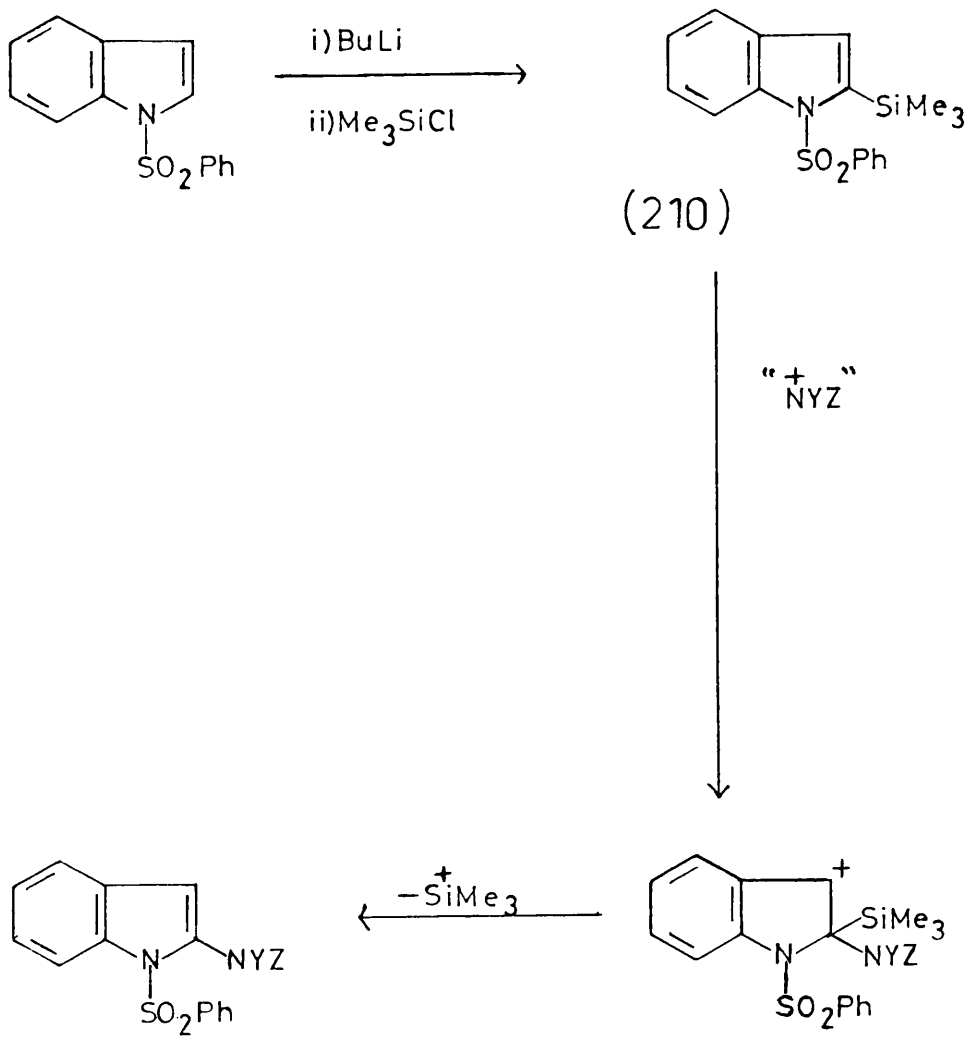
$$NO^- + BH \longrightarrow NOH + B^-$$

$$2NOH \longrightarrow H_2N_2O_2 \longrightarrow N_2O + H_2O$$

Scheme 45

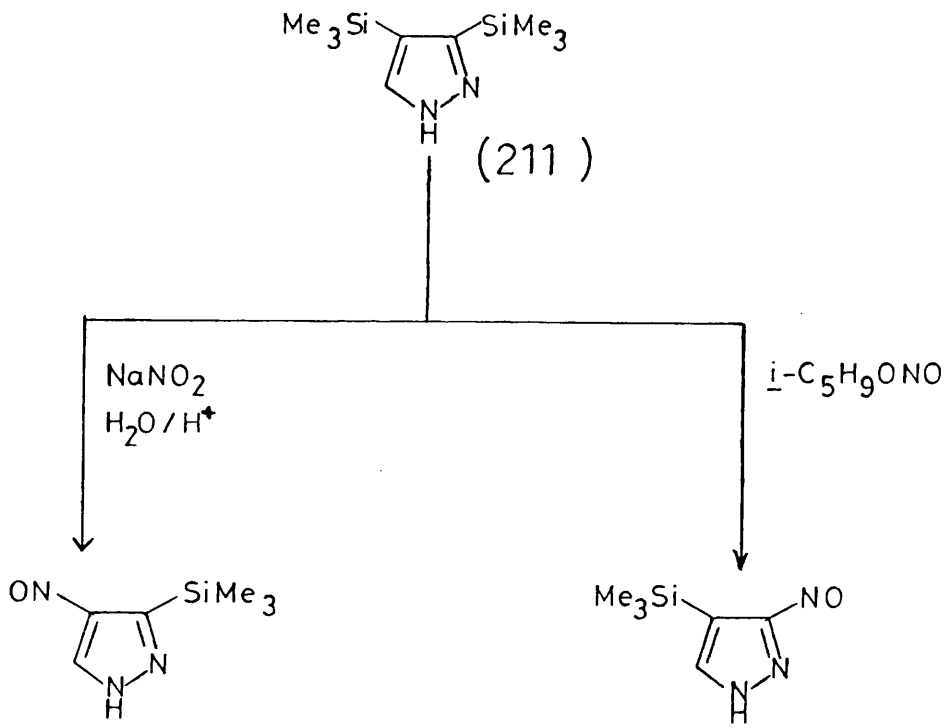
5.3 The reaction of *N*-phenylsulphonyl-2-trimethylsilylindole (210) with electrophiles

An alternative method of activating the indole-2- position towards electrophiles would be to form the 2-trimethylsilyl- derivative (Scheme 46). It is well known[116] that the trimethylsilyl group has a powerful *ipso* directing influence towards electrophiles. This effect is thought to be a result of the ability of silicon to stabilise a positive charge on an α-carbon atom. The magnitude of this effect can be gauged from the fact that the bromodesilylation of phenyltrimethylsilane demonstrates an *ipso* rate factor of 10^8.


i) BuLi
ii) Me_3SiCl
N
SO_2Ph
$SiMe_3$
(210)
"$\overset{+}{N}YZ$"
$-\overset{+}{S}iMe_3$
NYZ

Scheme 46

Examples of the reaction of silanes with nitrogen electrophiles were also encouraging. For example, 3,4-bistrimethylsilylpyrazole (211) may be mononitrosodesilylated, the regiospecificity depending on the conditions (Scheme 47).[117] Similarly,[116] phenyltrimethylsilane can be nitrodesilylated in good yields, although if strongly acidic conditions are used, protodesilylation predominates.



Scheme 47

We therefore synthesised *N*-phenylsulphonyl-2-trimethylsilylindole by treating 2-lithio-*N*-phenylsulphonylindole with excess trimethylsilyl chloride. Following work-up and flash chromatography on silica, the desired product was obtained in 61% yield. Examination of the ^{1}H n.m.r.

spectrum of the product showed that the effect of the silyl group was to cause the indole H-3 resonance to shift 0.35 p.p.m. downfield towards the aromatic region. Because of this, and because the possibility of a 1,2-silyl group migration was recognised, ^{13}C n.m.r. analysis was resorted to in order to confirm the structure (see Tables 3 and 4).

Aminative desilylation of the silylindole was attempted by stirring with MSH in dichloromethane at room temperature for 20 h, but t.l.c. analysis after this time revealed that amination had not taken place. Higher temperatures were not employed with this reaction because of the known explosive nature of the reagent.

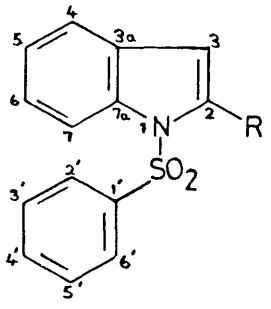
Effenberg[118] has recently described the use of potassium-*t*-butoxide as a catalyst for use with difficult electrophilic desilylations and for example, although 2-nitrophenyl(trimethyl)silane does not react with benzaldehyde even after heating at 100° C in DMF for three days, the addition of a catalytic quantity of *t*-butoxide results in substitution taking place at -60° C with the reaction being complete within 1 h. The exact mechanism of this catalysis is not certain, although it is possible that the base brings about nucleophilic desilylation to give the aryl anion in very low concentration. The fluoride ion mediated desilylation of arylsilanes and subsequent trapping of the anion with electrophiles if, of course, well known.[119] However, Effenberg's results do not conclusively support the nucleophilic desilylation mechanism.

In our case, the addition of a catalytic amount of potassium-*t*-butoxide to a mixture of *N*-phenylsulphonyl-2-trimethylsilylindole and MSH led to decomposition of the reagent. It therefore appears that even bases with p*K*α values as low as 17-20 are sufficient to bring about the deprotonation and consequent destruction of MSH.

As has been referred to above, isoamylnitrite has been employed in nitrosodesilylation reactions. A slight excess of the reagent was thus added to a solution of the silylindole in benzene and the resulting mixture heated at reflux for twenty-two hours. No products were detected after this time. The use of neat isoamylnitrite at

Table 3

^{13}C n.m.r. spectra of *N*-phenylsulphonylindoles

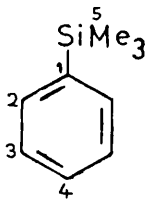


Position	Chemical shift values relative to TMS (p.p.m.)		
	(R = H)	(R = D)	(R = $SiMe_3$)
2	126.2	125.9 J_{C-D} = 223 Hz	143.1[b]
3	109.1	109.0 isotope shift = -0.18 p.p.m.	114.1[b]
3a	130.7	130.7	130.8[a]
4	123.3	123.3	123.3
5	124.5	124.5	125.0
6	121.3	121.3	121.8
7	113.4	113.4	121.0
7a	134.9	134.9	138.8[a]
1'	138.3	138.3	139.4[a]
2' and 6'	129.1	129.1	133.2[a]
3' and 5'	126.6	126.6	126.2
4'	133.6	133.6	129.0
R			$SiMe_3$ appears at 0.5

[a]Confirmed by long range coupling. [b]Assigned by comparison with the spectrum of phenyltrimethylsilane [(212) see Table 4].

Table 4

^{13}C spectrum of phenyltrimethylsilane



Position	Chemical shift (p.p.m.)	Substituent effect (*cf.* benzene)
1	140.5	+12.0
2	133.3	+4.8
3	127.8	+0.3
4	128.8	
5	-1.1	

reflux under a protective atmosphere of nitrogen for thirty-two hours led only to a small amount of the protodesilylated indole. Further boiling in the absence of nitrogen led to faster formation of the parent indole, possibly as a result of the presence of moisture in the air.

The sensitivity of the reagent towards alkoxide bases has already been described and for this reason Effenberg's catalysis conditions were not employed.

It was apparent at this stage that a more reactive electrophile was required. The silylindole was therefore treated with nitrosonium tetrafluoroborate in sulpholane at 30° C, but although t.l.c. analysis showed that reaction had occurred, the products appeared to be of a polymeric nature and no nitroso- or nitroindoles could be detected. ^{1}H n.m.r. spectroscopic analysis of the crude product proved fruitless. The reaction with nitronium tetrafluoroborate in dichloromethane solution was a little more successful. No reaction occurred between -78° C and -45° C, but at -20° C the emergence of a number of products was observed. Of these, the major component turned out to be *N*-phenylsulphonylindole, but after column chromatography a small amount of a nitrated product was obtained. However, what appeared to be a single compound was, on the basis of mass spectrometric examination, a mixture of mono- and di-nitrated products. In both cases the silyl group was retained and although the positions of nitration could not be proved conclusively, due to a lack of material for further analysis, it does seem that the combined effects of the phenylsulphonyl and trimethylsilyl groups are insufficient to overcome the natural tendency of the indole nucleus to undergo electrophilic substitution at the 3-position. The poor reactivity of the 2- position in this case may be partly due to the steric effect of the neighbouring phenylsulphonyl group.

In order to test the system further, the silylindole was treated with a number of non-nitrogen electrophiles. Accordingly, 1-phenylsulphonyl-2-trimethylsilylindole was heated with a large excess of benzaldehyde for fifteen hours. After this time the silylindole

remained intact, although some benzaldehyde decomposition products were observed. This failure correlates with the report of Thames *et al.*,[120] wherein 1-methyl-2-trimethylsilylpyrrole failed to react with benzaldehyde even after prolonged reflux. The 2- position of pyrrole is, of course, more reactive towards electrophiles than is the case with indole.

The silylindole was next reacted with one equivalent of bromine in carbon tetrachloride at 0° C. Again a mixture of products was obtained, of which unreacted starting material and *N*-phenylsulphonylindole were the major components. A quantity (≈10-15%) of a brominated product was also isolated, but although chromatographically homogeneous and possessing a sharp melting point, mass spectroscopic data showed it to be a mixture of mono- and di-brominated desilylated indoles.

The absence in the ^{1}H n.m.r. spectrum* of any significant peak above δ 7.2 suggests that bromination may have occurred at the β-position, although the alternative, bromodesilylation at the α-position, cannot be conclusively ruled out as the effect of a 2-bromo- substituent on the chemical shift position of the β-hydrogen is not known. The ^{1}H n.m.r. spectrum also shows a doublet at δ 8.32 which is significantly further downfield than the most deshielded hydrogens of either *N*-phenylsulphonylindole or the trimethylsilyl derivative. This indicates that the second bromination may have occurred in the benzene ring and the multiplicity of the signal makes it likely that substitution has taken place at the 5- position, or possibly the 6- position. If 3- substitution has occurred initially, then further bromination at the 4- position can be ruled out on steric grounds.[121]

The likely structures of the products are therefore (213) and (214) or (215) and presumably desilylation takes place through attack of Br^- or $Br^\cdot$ upon the silicon. Attempts to refine further the product by chromatography and recrystallisation were unsuccessful. "Constant melting" mixtures of bromoindole isomers have previously been reported by Da Settimo.[122]

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*See Figure 8.

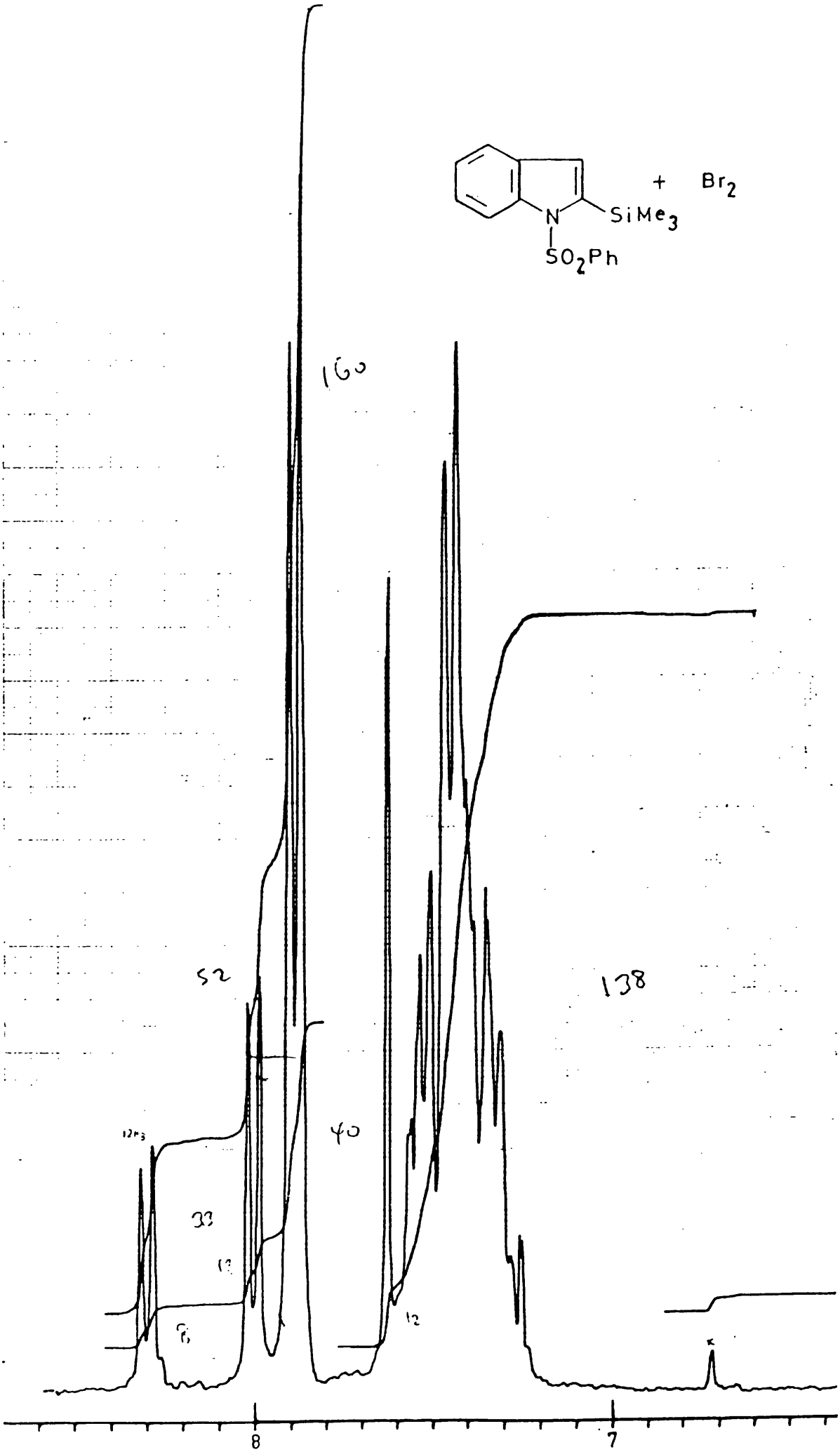
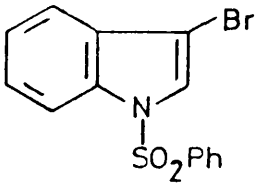
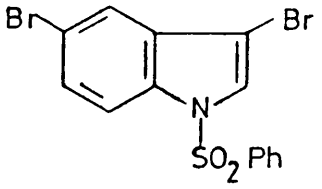


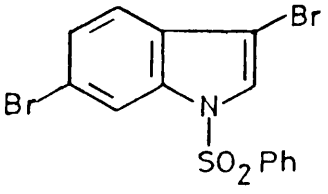
Figure 8



(213)



(214)



(215)

5.4 The synthesis and photochemistry of 2-benzoylaminoindoles

Before proceeding with further attempts to form *N*-substituted 2-aminoindoles and their precursors, we thought it prudent to test the second assumption upon which the overall synthetic scheme rested; namely that 2-aroylaminoindoles will undergo photochemically induced cyclisation to the α-carboline ring system.

The unprotected 2-aminoindole (201) was synthesised according to the procedure of Pschorr and Hoppe[108a] and thus 2-nitrophenylacetonitrile (216) was reduced with tin and hydrochloric acid to give 2-aminophenylacetonitrile (217) in the rather disappointing yield of 48%. Cyclisation to 2-aminoindole was accomplished by boiling the aminonitrile with a solution of sodium ethoxide in ethanol.* After work-up the aminoindole was obtained as a pale-green crystalline solid which rapidly acquired a dark-blue colouration on exposure to air. Decomposition was even more rapid in solution which rendered purification and characterisation very difficult.

The ^{1}H n.m.r. spectrum, run in d^4-methanol, showed only four aromatic proton resonances indicating that, in this solvent at least, interconversion of the three possible tautomers is occurring very rapidly.

The aminoindole was benzoylated using one equivalent of benzoylchloride in pyridine in the presence of a catalytic amount of *para*-dimethylaminopyridine. As expected, a mixture of products was obtained, the two major components being 2-benzamidoindole [(218), 35%] and 1-benzoyl-2-benzamidoindole [(220), 14%]. The use of two equivalents of the acid chloride resulted in a more complex reaction mixture but again, the major products were (218) and (220) in roughly the same ratio as obtained previously. It seems likely that aminoindole is initially monobenzoylated at both the 1- and *N'*- positions to give (218) and (219) respectively (Scheme 49). The ring benzoylated compound (219) may then be further acylated to give (220), but clearly higher temperatures and/or stronger bases are necessary before the isomer (218) undergoes reaction with the acylating agent.

Irradiation of a methanolic solution of 2-benzamidoindole (218) with 365 nm u.v. light in the absence of oxygen did not result in cyclisation to the α-carboline. This, we thought, might be due to the existence of an equilibrium between the uncyclised form [(198), R_1, R_2, R_3 and R_4 = H] and the cyclised dihydro intermediate [(1-9), R_1, R_2, R_3 and R_4 = H] which favours the starting materials, as is

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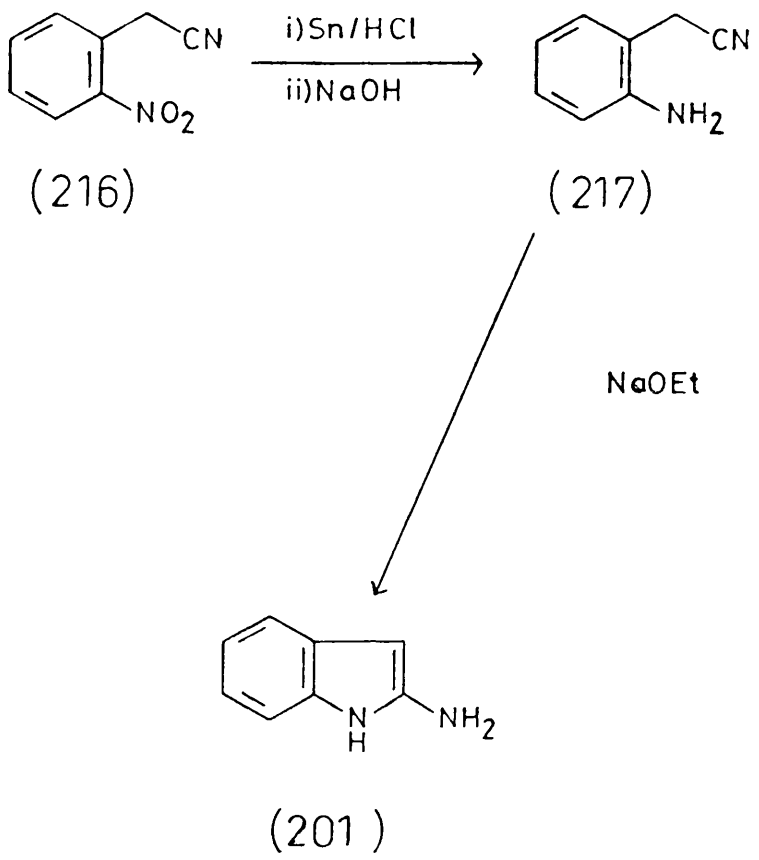
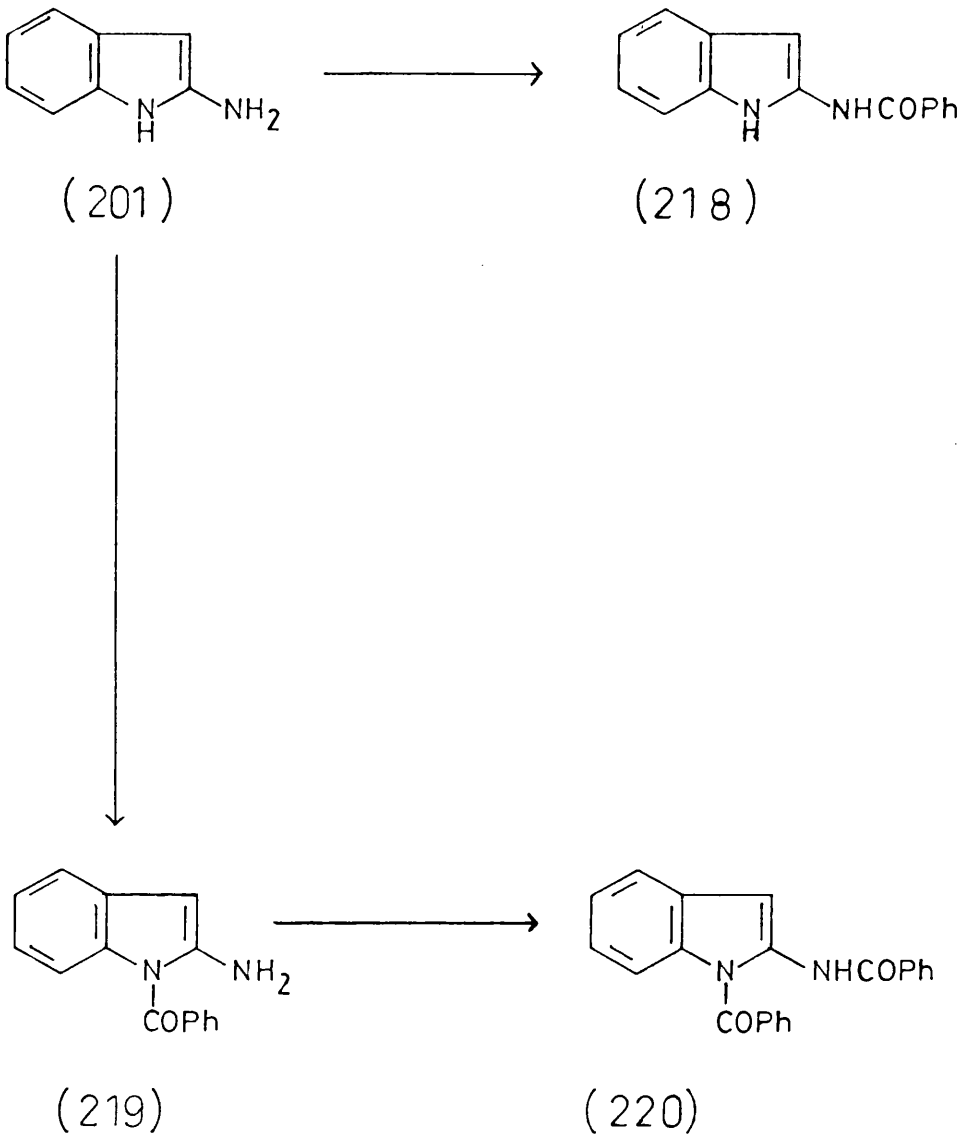
*See Scheme 48.



(216) (217) (201)

Scheme 48

observed in many related stilbene-phenanthrene cyclisations.[123] In such cases, the presence of an oxidant such as air or iodine is often required in order to bring about irreversible dehydrogenation and displacement of the equilibrium in favour or product. However, in the presence of air, the 2-benzamidoindole did not photocyclise; instead it underwent slow oxidative decomposition. This process was accelerated when iodine was added. Analysis of the photochemical

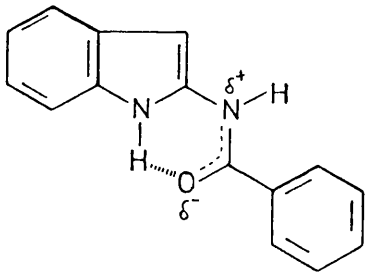


Scheme 49

reaction mixture after the addition of iodine revealed a number of products and a comparison with a sample of starting material treated with the oxidant, but not photolysed, showed that all of these products had arisen through iodine mediated processes.

The dibenzoyl analogue (220) proved much more stable to oxidising conditions but, once again, irradiation with u.v. light did not result in cyclisation, even after eighty-four hours. Instead, slow cleavage of the ring *N*-benzoyl linkage was observed with the resulting amide (218) decomposing as described above. Photosolvolyses of this type have previously been reported by Uttley.[124]

The failure of the monobenzoylated indole to undergo cyclisation may be due in part to strong intramolecular hydrogen bonding holding the molecule in a conformation (218a) from which cyclisation cannot



(218 a)

take place. The very low field position (δ 10.55) of the two N-H resonances in the ^{1}H n.m.r. spectrum indicates that they are relatively acidic, a fact which could be explained by hydrogen bonding of the type proposed.

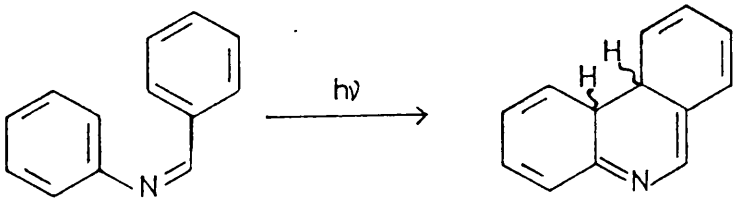
Intramolecular hydrogen bonding may also be envisaged as existing within the dibenzoyl derivative (220), but in this case the bonding would have the effect of holding the molecule in the correct conformation for cyclisation to occur. The fact that it does not take place is therefore surprising.

It has been reported[125] that aromatic Schiff bases will undergo photochemical cyclisation although, in some cases, a strongly acidic solution or the presence of a strong Lewis acid is required before reaction will proceed. For example, *N*-benzylideneaniline (221) can be cyclised to phenanthridine (223) although, interestingly, some benzylaniline (224) is formed through a disproportionation reaction involving the dihydro intermediate (222) (Scheme 50). The analogous compound, 2-benzalaminoindole (225) was therefore synthesised by treatment of a deoxygenated solution of 2-aminoindole in benzene with benzaldehyde. The resulting air sensitive solid proved to be insoluble in many of the common organic solvents, but was eventually characterised in the usual way through its ^{1}H n.m.r. spectrum and the i.r. spectrum which demonstrated the indole N-H stretching frequency at 3380 cm^{-1} and a resonance at 1635 cm^{-1} due to the C=N bond. In addition the mass spectrum showed a strong molecular ion at the required value of m/e 220.

The imine was suspended in dry deoxygenated benzene and subjected to u.v. irradiation for eighteen hours, but after this time it was apparent that cyclisation had not occurred. The use of aerobic conditions merely caused the compound to decompose slowly by oxidation.

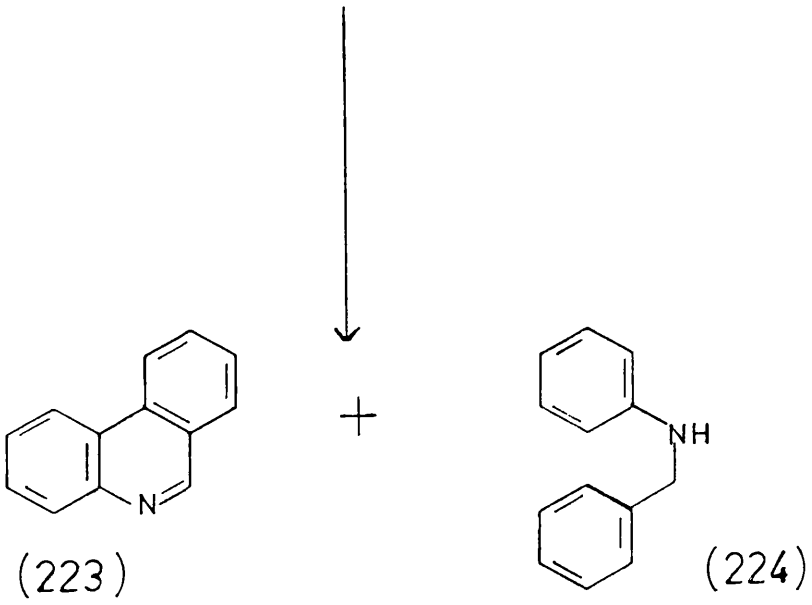
The failure of the imine to cyclise was not entirely unexpected since, as mentioned above, Schiff bases often require strongly acidic conditions to bring about ring closure. The sensitivity of indoles in general, and aminoindoles in particular, towards acids precluded the use of such conditions in our case.

In the case of *N*-benzylideneaniline, the poor reactivity in neutral solution has been attributed to internal conversion of the $\pi \rightarrow \pi^*$ state and to $n \rightarrow \pi^*$ state and to the very short lifetime of the *cis*-isomer from which cyclisation must occur. Similar effects may operate with the aminoindole Schiff base, although no hard evidence is available to support this proposal.



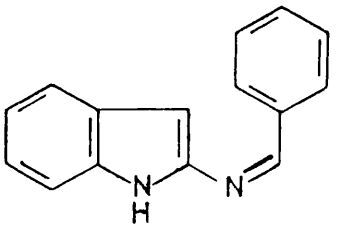
(221) (222)

(221) + (222)



(223) (224)

Scheme 50



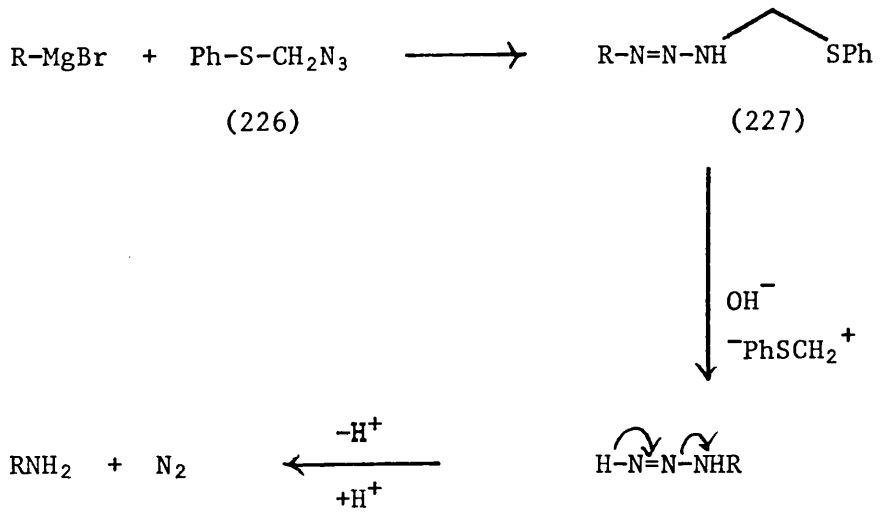
(225)

By this time it was becoming clear to us that the amination-aroylation-photocyclisation sequence was not going to provide the simple versatile synthesis of indolo[2,3-*b*]isoquinolines that we had hoped for. Even with further development it is difficult to see how the reluctance of the dienamides to photocyclise can be overcome without modifying the compounds to such an extent that the generality of the route is lost. We therefore reluctantly decided to draw this area of work to a close.

5.5 Azide based aminating agents

Although we had discontinued our efforts to synthesise indolo-[2,3-*b*]isoquinolines *via* aminoindoles, our interest was aroused by the appearance in the literature of several classes of aminating reagents, based on the azido function, which can be used in conjunction with organometallic species.

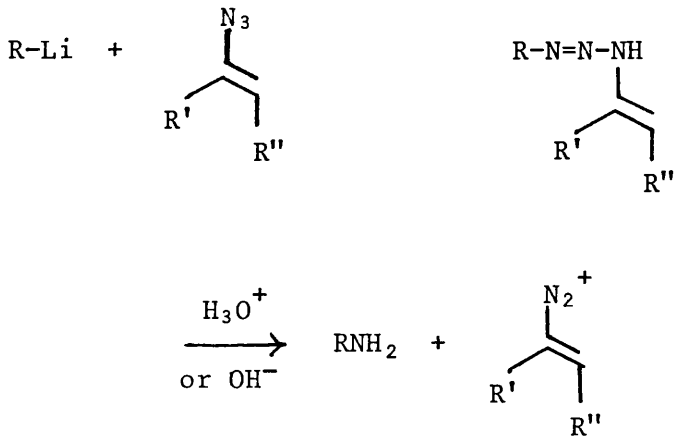
Trost[126] has described the use of azidomethylphenylsulphide (226) as a source of "NH_2^+". Treatment of Grignard reagents, usually formed by addition of magnesium bromide to a lithium compound, with this reagent leads to triazenes (227) which can be hydrolytically cleaved to give the amine (Scheme 51).



Scheme 51

Unfortunately, Trost reports that the application of this method to heteroaromatics such as furan, thiophene and indole was unsuccessful.

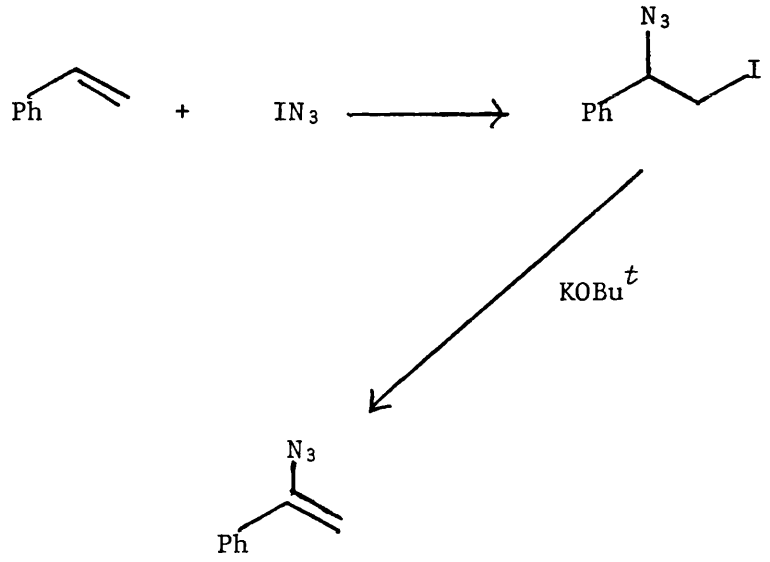
More recently, Hassner[127] has drawn attention to the use of vinyl-azides as aminating agents. These may be used in conjunction with aryl-lithium compounds to give triazenes which are again hydrolysed to the amine (Scheme 52).



Scheme 52

These reagents have been successfully employed in the amination of a number of heteroaromatics including 2-methylthiophene and benzthiazole, but no reaction with lithioindoles has been reported. We therefore set out to determine whether this reagent can be applied to the synthesis of 2-aminoindoles.

The aminating agent was made according to Hassner's method (Scheme 53)[128] and thus iodine azide, generated in acetonitrile solution



Scheme 53

by addition of iodine monochloride to sodium azide, was treated with styrene to give 1-azido-2-iodo-2-phenylethane in 58% yield. Reaction of this compound with potassium-*t*-butoxide caused elimination of hydrogen iodide to give the desired product in approximately 50% yield after chromatography on alumina.

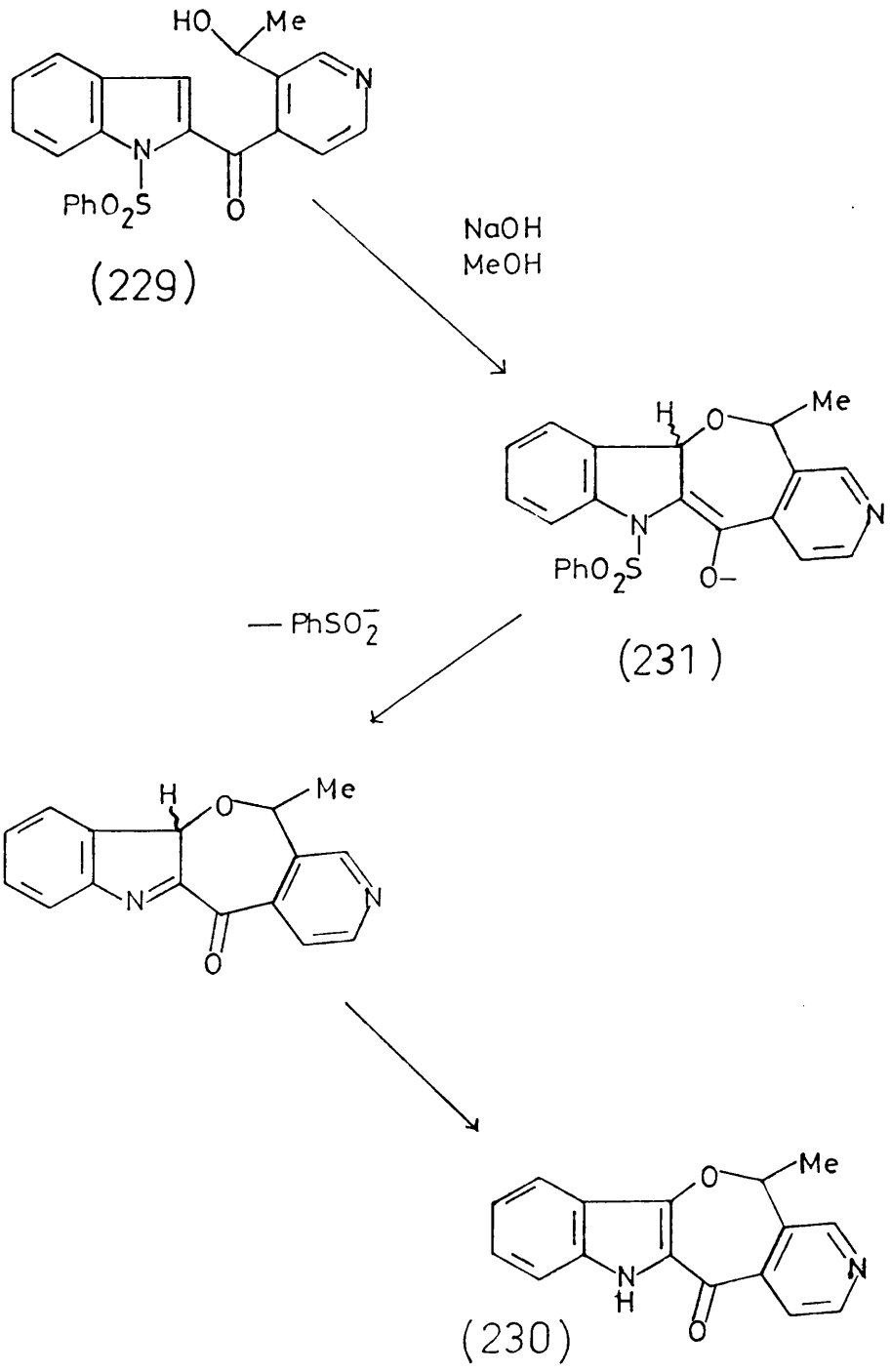
The azide (228) was added to a cold solution of 2-lithio-*N*-phenylsulphonylindole in THF and the solution allowed to warm gradually to room temperature. After two hours the reaction reached a standstill with a considerable amount of starting material present and very little product. A hydrolytic work-up failed to produce any aminoindole and, moreoever, the oxidation products which might have been formed had the phenylsulphonyl group been cleaved from the anticipated aminoindole were also not in evidence.

It is conceivable that the failure of this amination procedure is a result of the *N*-phenylsulphonyl group having too great a stabilising influence on the lithiated indole, thereby reducing its reactivity towards the azide. If this is so, then the problem could be overcome by using an indole bearing a substituent, such as *N*-methyl, which does not exert such a powerful stabilising effect. However, by this time our priorities lay elsewhere and the matter was not pursued. In any case, 2-amino-*N*-methylindole has been synthesised more expeditiously by treatment of 2-aminophenylacetonitrile with methyliodide.

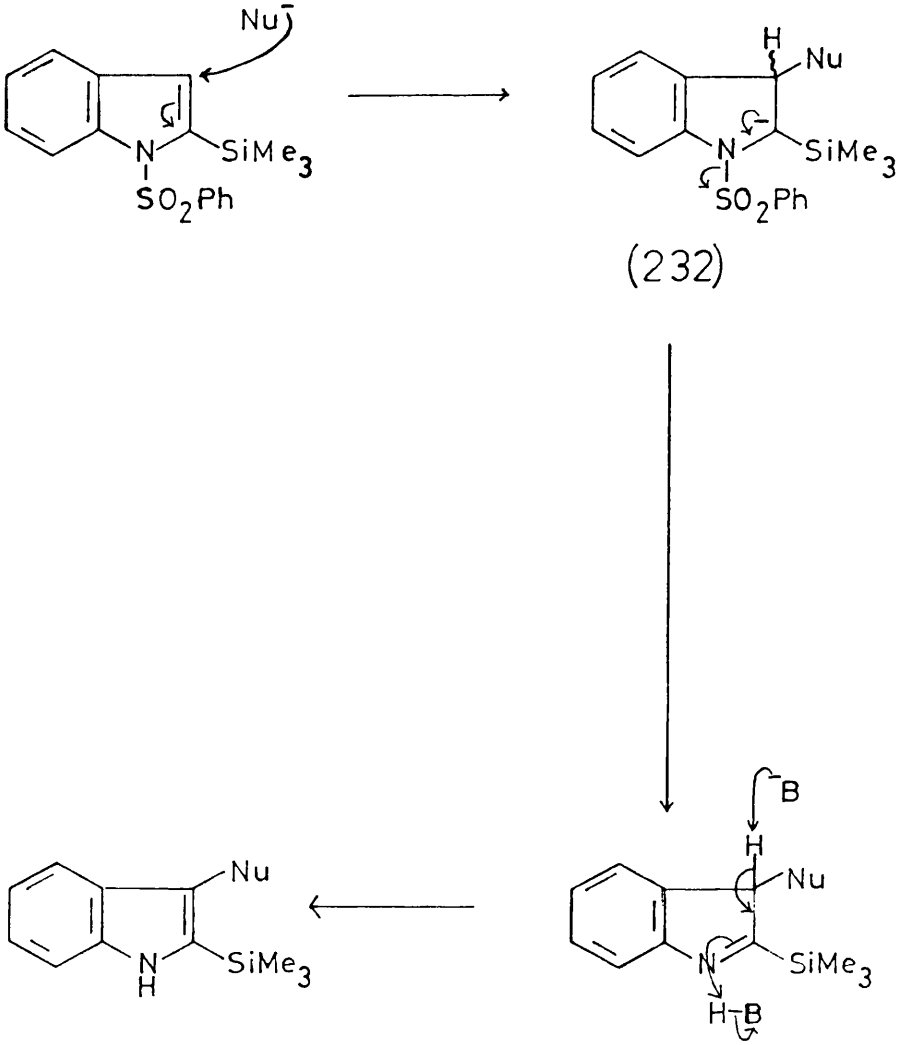
5.6 The reaction of 1-phenylsulphonyl-2-trimethylsilylindole with nucleophiles

A rare example of nucleophilic attack at the β-position of the indole nucleus has recently been reported by Joule[129] (Scheme 54). During an attempt to cleave the *N*-phenylsulphonyl linkage in the hydroxyketone (229) with sodium hydroxide, the oxepinoindole (230) was formed unexpectedly. This was judged to have arisen by intramolecular nucleophilic attack of the alkoxide oxygen upon the indole-β- position to give the enolate intermediate (231), followed by elimination of phenylsulphinate ion and tautomerisation to the product (230). It is also conceivable that nuclephilic attack and departure of the phenylsulphinate ion constitute a synchronous process. It was subsequently found that the carbonyl group was essential for the activation of the β-position.

The ability of the second and third row elements, *e.g.*, sulphur and phosphorus to stabilise α-carbanions is well known.[130] We therefore considered the possibility that 1-phenylsulphonyl-2-trimethylsilylindole might act as a substrate for β-nucleophilic attack, the rationale being that the silicon atom would help stabilise the hypothetical intermediate [(232), see Scheme 55]. If successful, this scheme would have the added advantage that silicon-carbon bonds are readily cleaved under mild conditions which means that the directing group could be removed easily once it had outlived its usefulness.


HO
Me
N
N
PhO2S
O
(229)
NaOH
MeOH
H
O
Me
N
N
PhO2S
O−
(231)
— PhSO2−
H
O
Me
N
N
O
Me
O
N
H
N
O
(230)

Scheme 54



(232)

Scheme 55

As expected, the reaction of 1-phenylsulphonyl-2-trimethylsilylindole with fluoride ion (in the form of tetra-*n*-butylammonium fluoride) resulted in quantitative desilylation to yield *N*-phenylsulphonylindole. Desilylation was also observed when the silylindole was treated with sodium methoxide in methanol, although reaction was much slower in this case. No β-nucleophilic substitution was observed.

In an attempt to introduce a 3-amino function, the substrate was stirred with diethylamine at room temperature overnight. No reaction was observed and this was also the case after prolonged reflux.

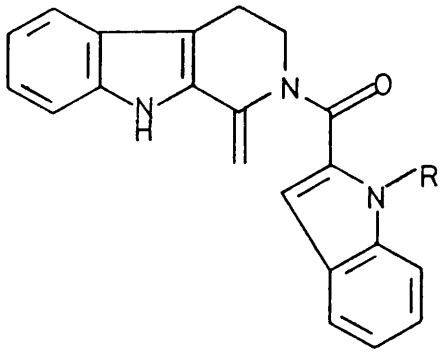
Finally, the sodio- derivative of diethylmalonate, formed by addition of sodium hydride to malonic ester, was reacted with the trimethylsilylindole. After stirring at room temperature for ten hours, it was apparent that desilylation was once again taking place. This process was accelerated by heating and after work-up a good yield of *N*-phenylsulphonylindole was isolated.

In conclusion, it appears that of the three possible electrophilic sites on the molecule, the silicon atom is the most susceptible to nucleophilic attack and is thus of no use as a directing group. It is likely that a more electron withdrawing group is required at the 2- position in order to polarise the double bond sufficiently for nucleophilic attack to occur.

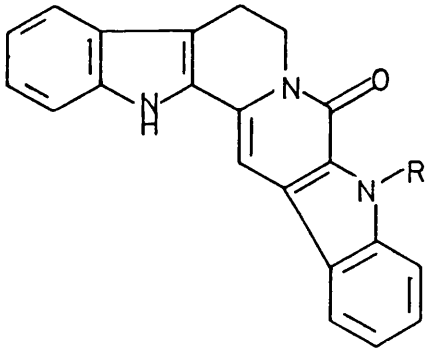
5.7 The synthesis of some bisindoloquinolizines

By virtue of their planarity and similarity[131] to other classes of compound known to intercalate with molecules of DNA, the two bisindoloquinolizines (234) and (236) might be expected to demonstrate anti-cancer activity.

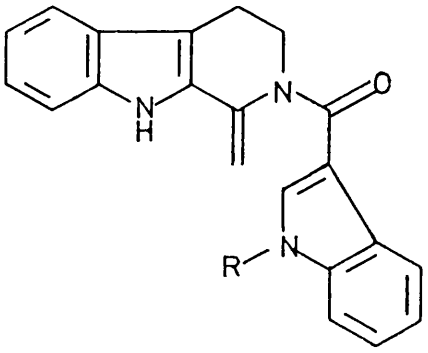
In principle, the two novel ring systems could be synthesised by photocyclisation of the dienamides (233) and (235). Formation of the dienamides (233) and (235) should take place readily by the acylation of harmalan (153) with appropriately substituted indole-2- and indole-3-carbonyl chlorides respectively. The starting material common to both syntheses, harmalan (153), was obtained *via* the Bischler-Napieralski procedure (Scheme 56).[132]



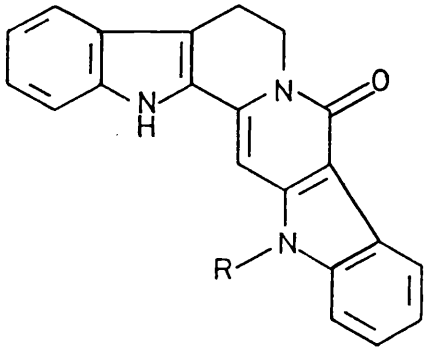
(233)



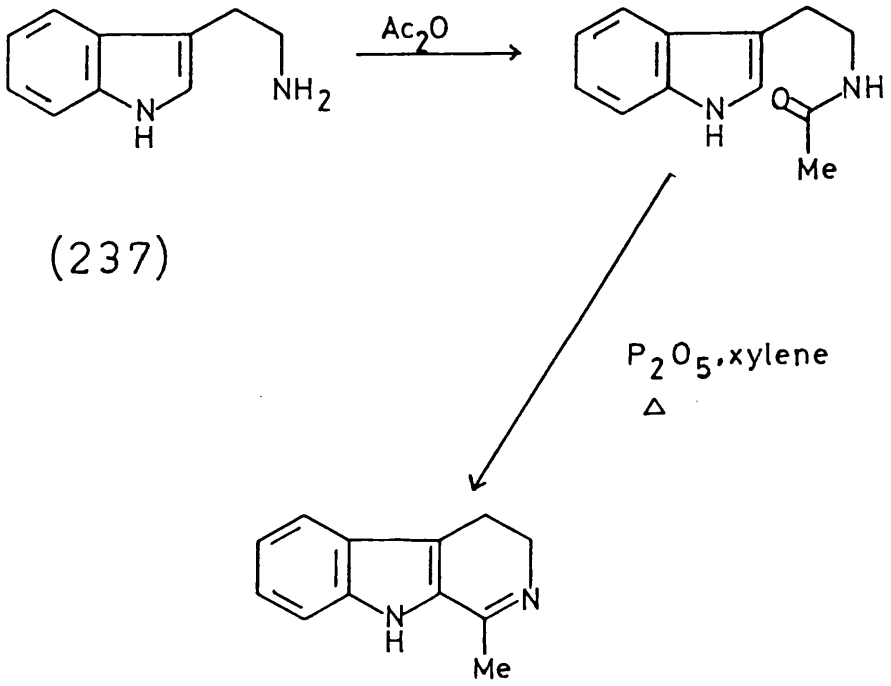
(234)



(235)



(236)



(237)

(153)

Scheme 56

Tryptamine (237) was thus acetylated with acetic anhydride in ethanol at room temperature to give, after work-up, *N*-acetyltryptamine in 94% yield. Cyclisation of the *N*-acetyl derivative in approximately 70% yield was achieved using phosphorus pentoxide in boiling xylene. This latter reaction, which is heterogeneous, is cumbersome and involves a huge excess of reagent in conjunction with relatively large volumes of solvent. Phosphorus oxychloride has been employed in many ring closures of a similar type[132] and has the twin advantages of acting under homogeneous conditions and requiring only an approximate six-fold

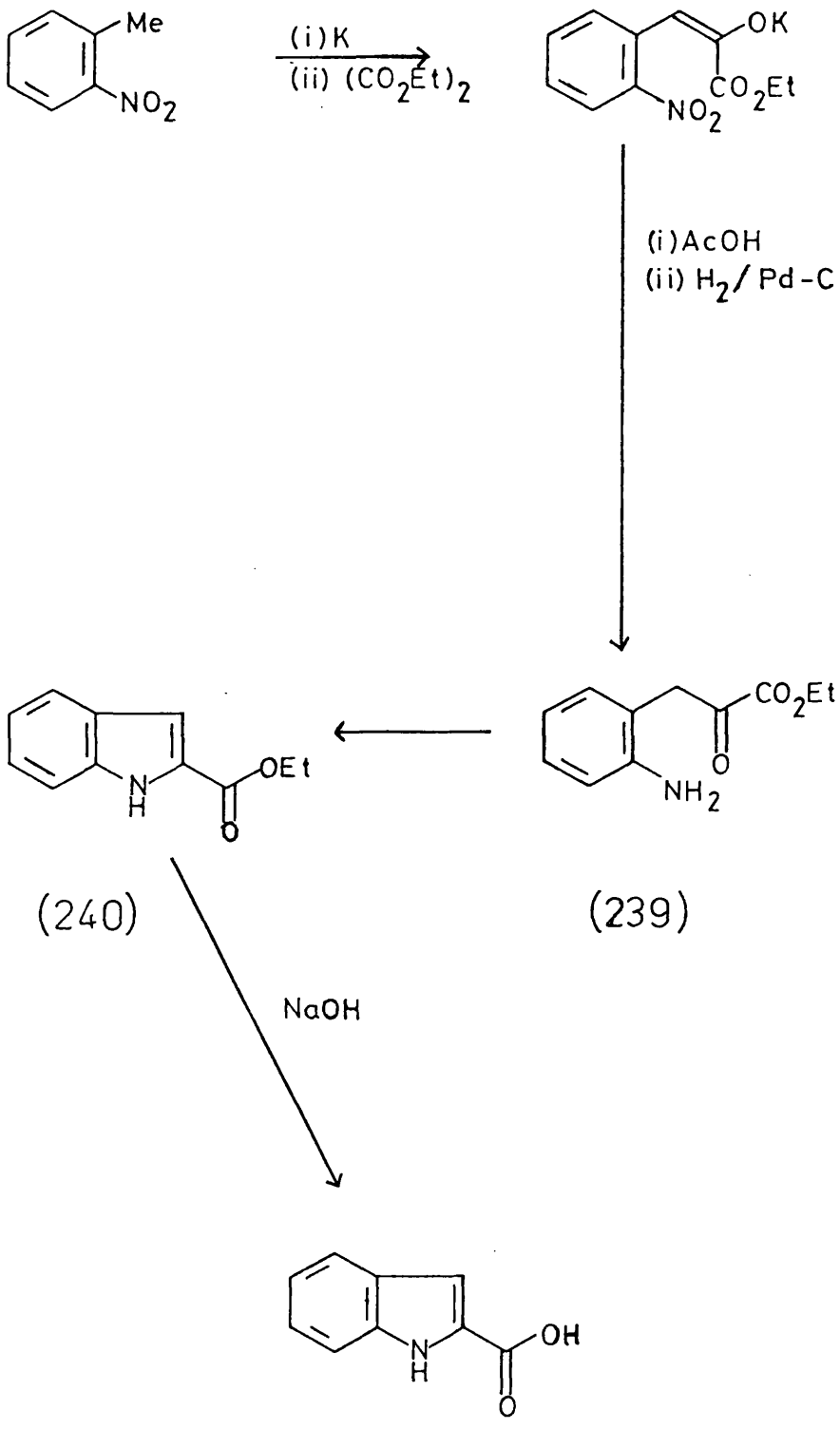
excess, as opposed to the fifty-fold excess recommended for many phosphorus pentoxide cyclodehydrations. However, the use of phosphorus oxychloride in the cyclisation of *N*-acetyltryptamine to harmalan resulted in the formation of only low yields of the desired product. Moreover, the side products were more numerous, thereby creating an isolation problem.

Synthesis of the other half of the projected indole-2-carbonyl-dienamide (233) was accomplished using a modified Reissert reaction[133] (Scheme 57). This sequence involved the initial metallation of 2-nitrotoluene with potassium, followed by treatment with diethyl oxalate to give the potassium enolate salt of ethyl-3-[2'-nitrophenyl]-pyruvate (238). Hydrogenation in acetic acid using either palladium on charcoal or platinum catalysts yielded the amine (239) which spontaneously cyclised to give ethyl indole-2-carboxylate (240). The ester was hydrolysed to indole-2-carboxylic acid by heating in 2 N sodium hydroxide at 95° C.

Several methods[134] of preparation of indole-2-carbonyl chloride have been described, but the mildest and seemingly most convenient[134a] involves simply treating the acid with thionyl chloride in ether at room temperature. Residual reagent and hydrogen chloride are subsequently removed by co-evaporating several times with dry ether.

Using this method, the acid chloride was obtained as an air sensitive canary-yellow solid which was characterised from its mass spectrum and by formation of the anilide derivative. It was found, however, that conversions were rarely as high as the 80-90% quoted in the literature[134a] and in general, considerable quantities (usually approximately 30%) of unreacted acid remained.

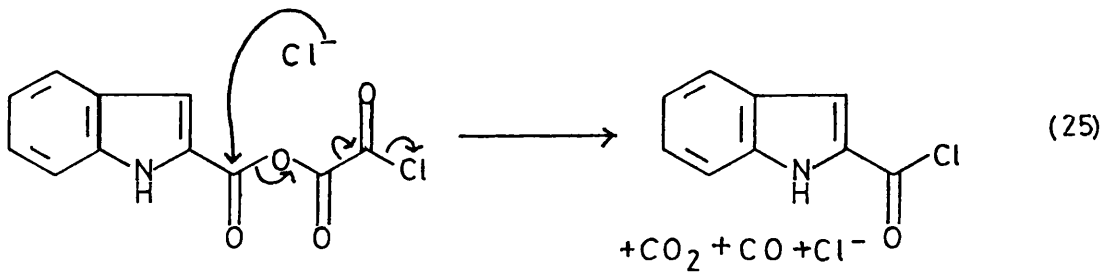
A solution of the acid chloride in dichloromethane was added to a mixture of harmalan and triethylamine in the same solvent, but after stirring at room temperature for two hours no significant product formation was observed. Heating the reactants to reflux similarly failed to result in formation of the desired product, although the solution darkened, indicating that a reaction was taking


Me
NO2
(i)K
(ii) (CO2Et)2
OK
CO2Et
NO2
(i)AcOH
(ii) H2/Pd-C
CO2Et
O
NH2
OEt
N
H
O
(240)
(239)
NaOH
OH
N
H
O

Scheme 57

place. Although t.l.c. analysis showed that a considerable quantity of harmalan remained, only a trace of indole-2-carboxylic acid was present, but because the method of preparation of the acid chloride was not totally efficient, it was not clear whether the acid was present through hydrolysis on the t.l.c. plate of unreacted acid chloride, or whether it was simply a result of incomplete conversion to the acid chloride in the preceding stage.

In order to resolve the ambiguity, an alternative preparation of indole-2-carbonyl chloride was utilised. Treatment of an aqueous acetone solution of indole-2-carboxylic acid with crushed sodium hydroxide pellets, followed by evaporation of the solvent, afforded sodium indole-2-carboxylate. The dried salt was suspended in benzene or dichloromethane and oxalyl chloride added. Gentle warming resulted in elimination of carbon monoxide and carbon dioxide, presumably from the intermediate (241) to give the acid chloride [equation (25)].

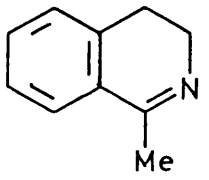


(25)

(241) (242)

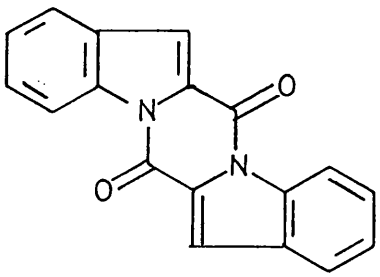
Addition of the acid chloride to solutions of harmalan in dichloromethane, containing either triethylamine or pyridine and the acylation catalyst 4-dimethylaminopyridine, again failed to result in dienamide formation. This time, however, t.l.c. analysis showed only harmalan along with baseline material. Even when very polar

eluents were used (*e.g.*, MeOH, $CHCl_3/NEt_3$), no derivatives of indole-2-carbonyl chloride were observed and it is therefore apparent that the acid chloride had been consumed during the reaction. A similar result was obtained from the attempted acylation of the isoquinoline imine (243) with indole-2-carbonyl chloride in the presence of triethylamine.

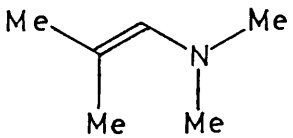


(243)

A likely explanation for the failure of the acid chloride to couple with harmalan is that in the presence of strong bases, it undergoes self condensation to give the dimeric compound (244). Boatman and Whitlock[135] have reported that this species is formed as a side product when the indole-2-acid chloride is reacted with two equivalents of the enamine (245). If triethylamine is used as



(244)



(245)

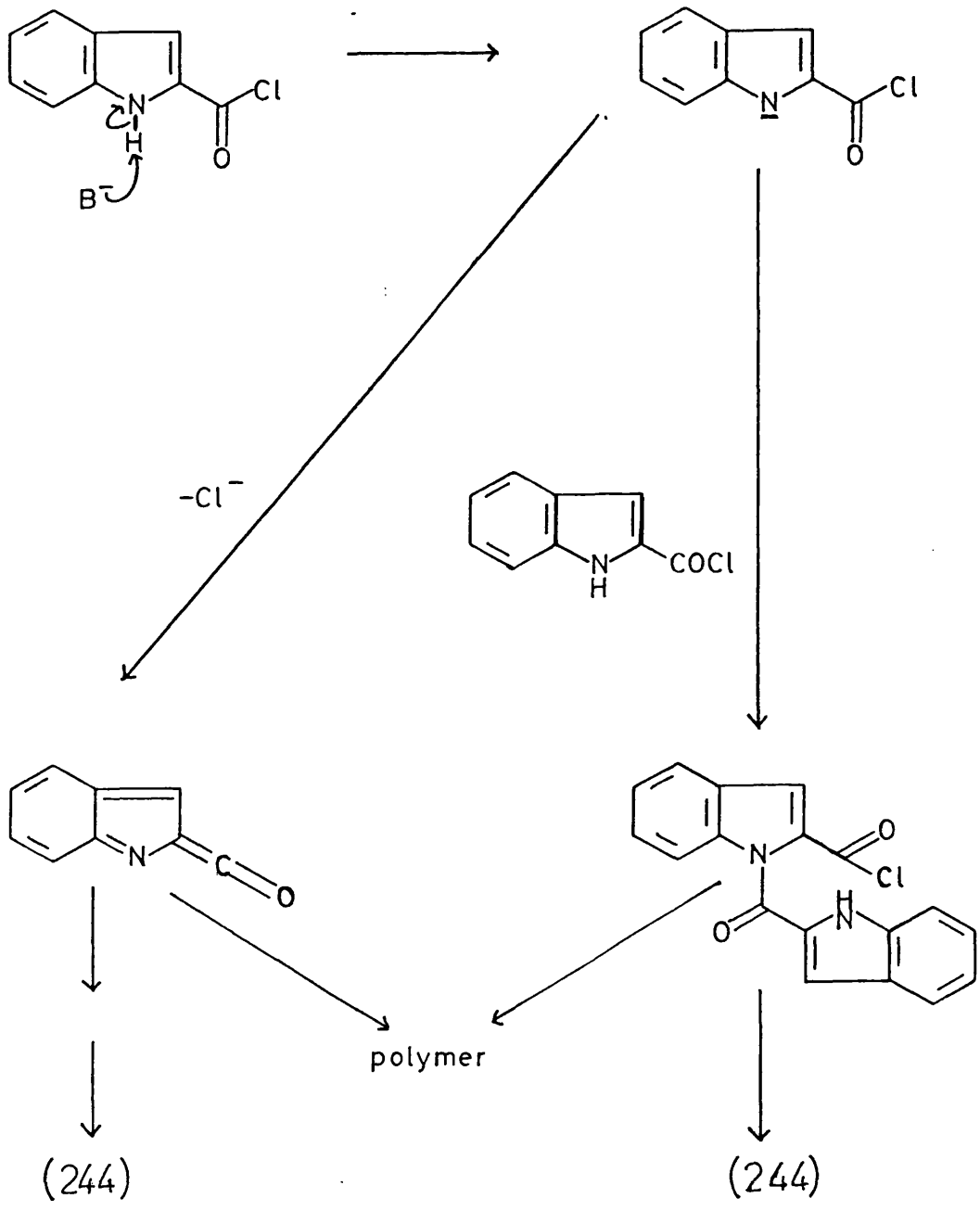
the base, the dimer becomes the major product. Formation of the dimer may also explain the low yields of amides obtained by other workers[134a] when reacting the acid chloride with various simple amines. The self condensation product has also been shown to arise when indole-2-carboxylic acid is treated with acetic anhydride.[136]

The dimeric species (244) may be envisaged as forming *via* initial deprotonation of the indole followed by attack of the anion upon another molecule of acid chloride (see Scheme 58). Alternatively, a mechanism involving the intermediacy of the keten (246) could be postulated, although this seems less likely, since it would involve disrupting the aromaticity of the carbocyclic ring.

In an attempt to sidestep the problem of self condensation, harmalan and ethyl indole-2-carboxylate were heated together in benzene at reflux for fifteen hours, but no reaction was observed to occur during this time.

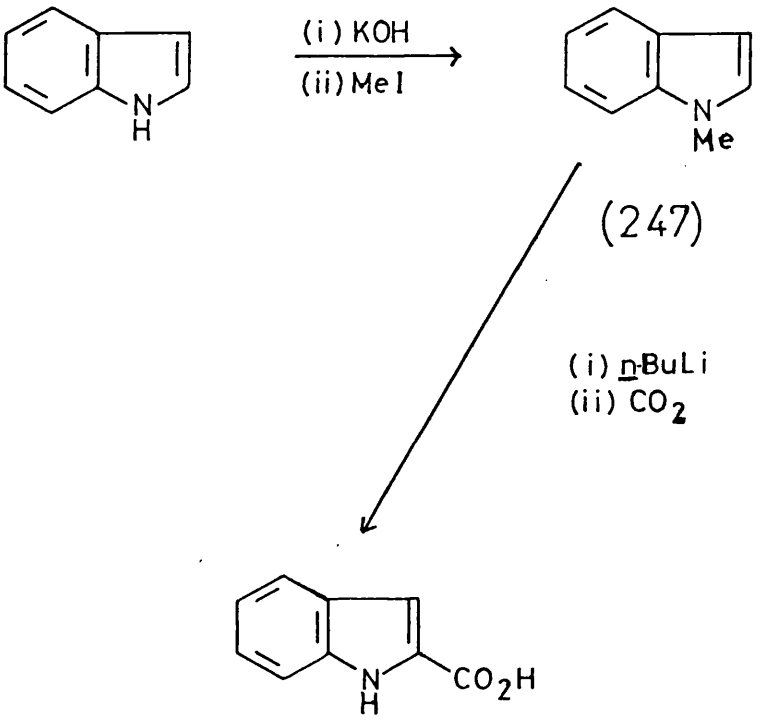
The problem of acid chloride decomposition was finally countered by using the *N*-protected acid chloride. Initially the *N*-methyl derivative was chosen both for its ease of preparation (Scheme 59) and for the minimal steric influence that the methyl group would exert on any subsequent photocyclisation.

Indole was thus *N*-methylated[137] by formation of the indole anion with potassium hydroxide in acetone followed by the addition of methyl-iodide. After column chromatography the *N*-methyl derivative (247) was obtained in a yield of 85%. Lithiation[111] of *N*-methylindole was accomplished by reaction with *n*-butyl-lithium in THF at room temperature and the resulting 2-lithioindole was quenched with dried carbon dioxide gas to give *N*-methylindole-2-carboxylic acid (248) in 41% yield. Formation of the acid chloride of (248) was achieved under very mild conditions by addition of one equivalent of oxalyl chloride to a suspension of the acid in dichloromethane in the presence of a catalytic amount of dimethylformamide. The resulting mixture was stirred until no further evolution of gas was observed and then added to a solution of harmalan and triethylamine in dichloromethane. This time, within minutes, formation of a product was observed, and



Possible decomposition pathways for indole-2-carbonyl chloride

Scheme 58



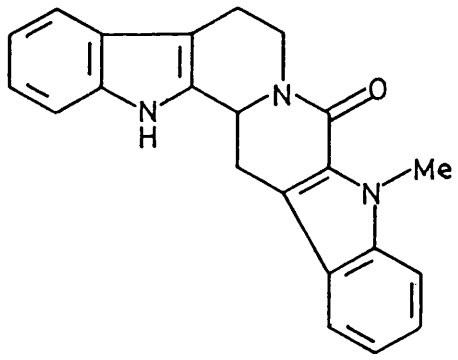
Scheme 59

after work-up and flash chromatography the relatively unstable dienamide [(233), R = CH_3] was obtained as a yellow gum.

The dienamide [(233), R = CH_3], which was characterised by the usual spectroscopic and spectrometric methods, was dissolved in dry deoxygenated benzene and subjected to irradiation with u.v. light at 365 nm for fifteen hours. After purification by further chromatography the aromatised polycycle [(234), R = CH_3] was obtained as a

pale-yellow crystalline solid in an overall yield from harmalan of 38%. Solutions of the polycycle, which dissolved with extreme reluctance in the common organic solvents, where highly fluroescent.

In a subsequent photocyclisation the initial photolysis product, the non fluorescent dihydro derivative (249), was isolated along with



(249)

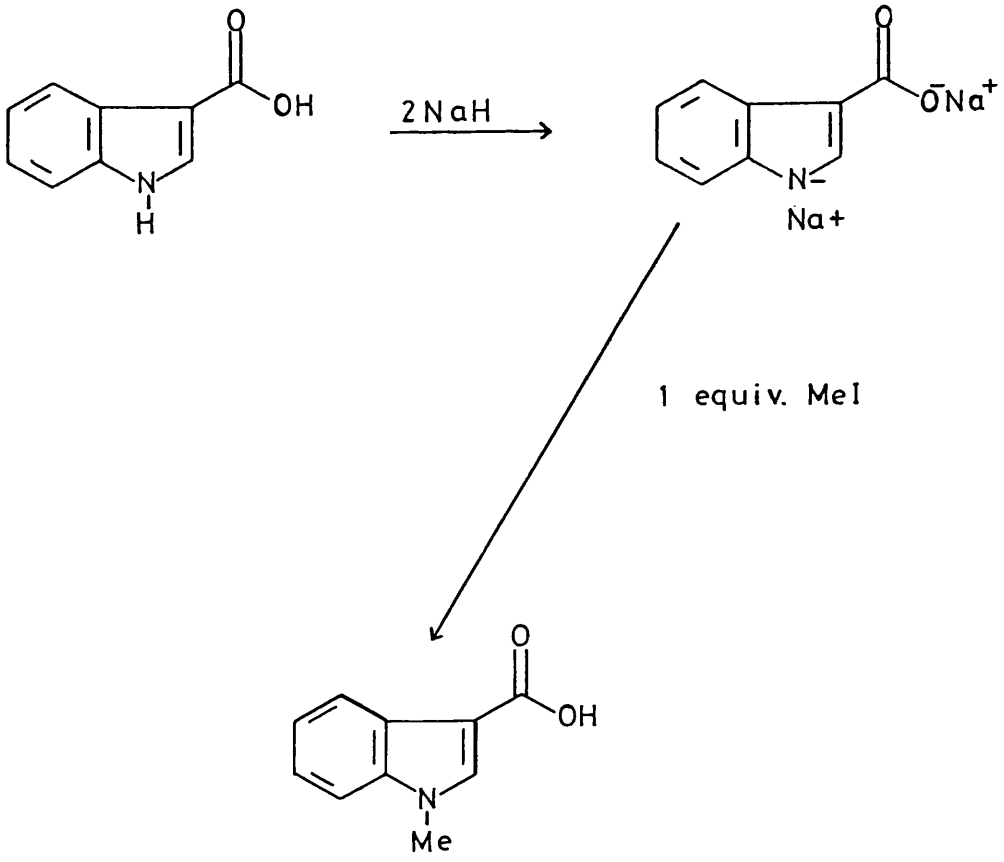
[(234), R = CH_3]. Aromatisation of this species occurred fairly readily on silica, although solutions appeared to be stable for some time.

In parallel with the attempts to couple harmalan with indole-2-carbonyl chloride, the synthesis of indole-3-carboxylic acid chloride was also investigated. This compound has received relatively little literature coverage, although several syntheses have been reported. Peterson[138] has reported that the acid chloride is formed through loss of carbon monoxide from indolyl-3-glyoxylyl chloride when the latter is heated at 115° C. However, yields are low (16-23%) and the major product appears to be a condensation product which is hydrolysed to indole-3-carboxylic acid by alkali.

Bergman[139] has described the reaction of phosgene with indole to give the 3-acid chloride directly, and a number of esters and amides have been made in good yield by this route. Significantly, the yields of amide derivatives formed from *N*-unsubstituted acid chlorides are lower than with the analogous *N*-blocked acid chlorides. This was in keeping with the observations of Wormser,[140] who reacted indole-3-carbonyl chloride with a variety of amines, but was unable to obtain amides in greater than 50% yield. Nevertheless, the reasonable yields of indole-3-carbonyl derivatives reported by Bergman[139] prompted us to use his approach. Accordingly, a commercial solution of 12.5% phosgene in toluene was added carefully to a cooled solution of indole and pyridine in toluene but, much to our consternation, rapid tar formation was observed. The addition of ethanol and aniline to solutions prepared in this way did result in the formation of the ethyl ester and anilide respectively, but the yields were not good and the crude reaction product required chromatographic purification rather than the simple recrystallisation recommended in the literature. The use of scrupulously dried toluene and pyridine made little difference and eventually the unsatisfactory nature of the reaction was attributed to the poor quality of the commercial phosgene solutions. It is noteworthy that Bergman's syntheses were carried out with freshly prepared phosgene solutions, a facility that was not available to us at that time.

N-Unsubstituted indole-3-carbonyl chloride, in which the nitrogen is in more direct conjugation with the carbonyl function, would be expected to show greater N-H acidity than indole-2-carboxylic acid chloride. The dangerof base induced self condensation is therefore potentially greater. This hypothesis is supported by the low yields obtained by several workers when reacting the 3-acid chloride with amines.[138,140] In view of this, and in the light of our experience with the indole-2-acid chloride, it was decided that we should abandon attempts at coupling the unprotected indole-3-carbonyl chloride, but should concentrate instead upon the *N*-methyl derivative.

N-Methylindole-3-carboxylic acid (250) was prepared from indole-3-carboxylic acid by initial formation of the dianion, through addition of two equivalents of sodium hydride to a solution of the acid in dichloromethane/dimethylformamide, followed by the addition of one equivalent of methyliodide (Section 60). Methylation occurred preferentially at the more reactive *N*-position to give (250) in 74% yield.



(250)

Scheme 60

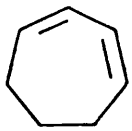
Acid chloride formation was achieved in the same manner as for the indole-2-carboxylic acid, namely by the use of oxalyl chloride in the presence of a trace of dimethylformamide. Formation of the dienamide [(235), R = CH_3] occurred readily when the acid chloride was added to a dichloromethane solution of harmalan and a slight excess of triethylamine. However, the dienamide was accompanied by a considerable quantity of a polymeric material. This is in accordance with Bergman's observation[139] that 2-unsubstituted 3-indolyl acid chlorides may undergo self condensation or polymerisation unless a large excess of base is present.

The dienamide, which was unstable to chromatography on silica and alumina, was subjected to photolysis in the crude state. After irradiation of a benzene solution at 365 nm for approximately twenty hours and subsequent chromatography, the aromatised product [(236), R = CH_3] was obtained as a highly insoluble microcrystalline solid in the rather disappointing yield of 15% overall from harmalan. The diminished yield may be attributed to the instability of the intermediate dienamide and also, possibly, to the interference in the photochemical process by impurities in the crude reaction mixture.

5.8 Extension of the dienamide method to novel ring systems

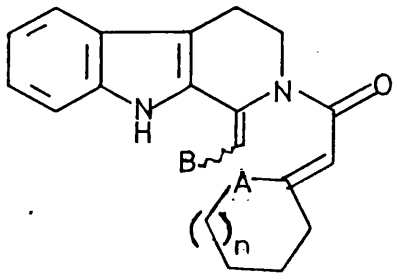
By modifying the components of the dienamide system and by exploiting the mechanistic features of the photocyclisation, it should be possible to extend the dienamide ring closure to give products other than the fused ring pyridone systems which are generally obtained. Several ways of doing this spring readily to mind. By substituting a cyclopropyl group for a double bond, photochemical or thermal cyclisation would result in formation of fused azepinones. Simple azepinones have previously been synthesised[141] by thermal cyclisation of isocyanate substituted cyclopropanes. In addition, the all carbon analogue, divinylcyclopropane (251) cyclises under both thermal and photochemical conditions to give the cycloheptadiene (252).[142]

(251)

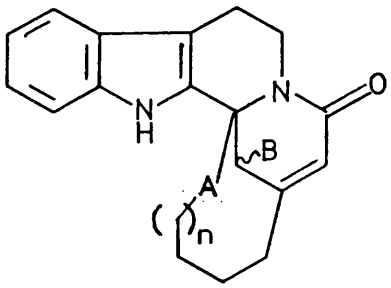


(252)

A second possible variation makes use of the [1,5]-sigmatropic migration which generally takes place after the initial cyclisation. For example, photochemical or thermal ring closure of the dienamide (253) could conceivably be followed by migration of either the Z-type (migration of A) or X-type (migration of B).



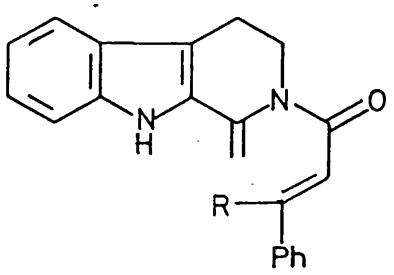
(253)



(263)

If A could be persuaded to migrate, the result would be the formation of an interesting new range of bridged indole polycycles.

To test this proposal using a simple model, dienamides of the type (254) were subjected to photolysis. The choice of the cinnamoyl group, which was not a random one, was made to give us the option of either photochemical or thermal cyclisations, since dienamides containing the cinnamoyl moiety have been observed to cyclise readily under thermal conditions.

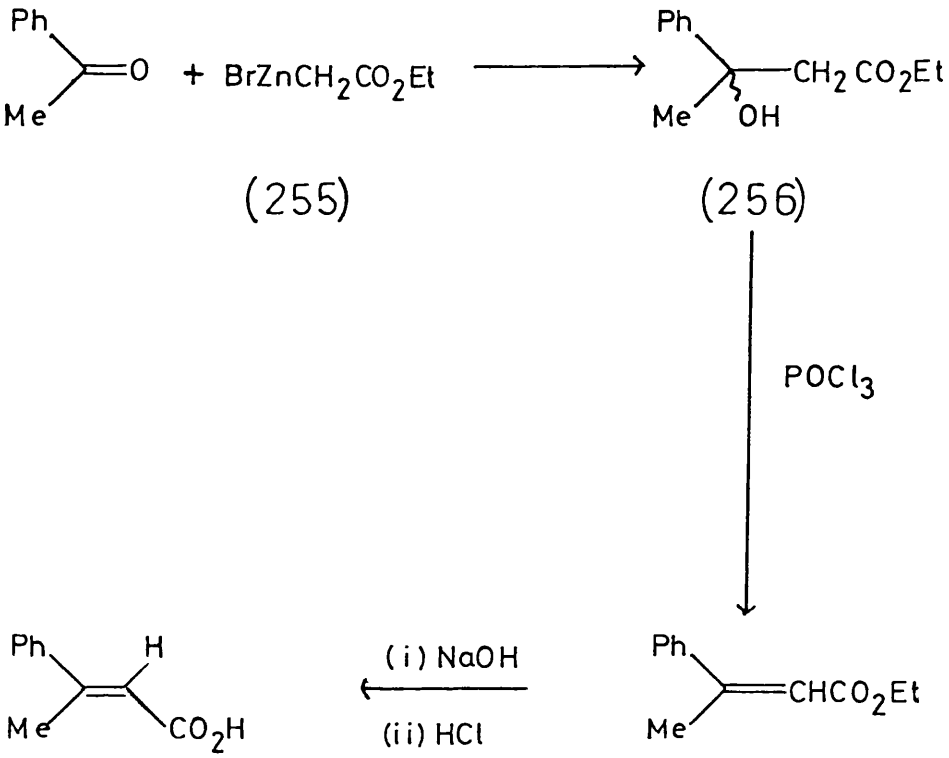


(254)

The first target to be synthesised was the β-methylcinnamoyl derivative [(254), R = CH_3], the simplest R-substituted dienamide of the series. As β-methylcinnamic acid is not available commercially, the enacyl half of the dienamide was synthesised by the Reformatsky reaction (Scheme 61).[143] Thus the organozinc reagent (255) was formed by treating ethylbromoacetate with zinc and was then allowed to react with acetophenone to give the hydroxyester (256). Dehydration of the hydroxyester was achieved using phosphorus oxychloride in boiling toluene to give exclusively the *trans*-β-methylcinnamic ester (257).

Hydrolysis to the *trans*-acid was accomplished by heating the ester in 2 N sodium hydroxide solution. Upon acidification, β-methylcinnamic acid was obtained in an overall yield from acetophenone of 14%. The low yield can be attributed to incomplete formation of the zinc reagent and to a poor recovery of product from vacuum distillation of the ester.

Formation of the acid chloride was achieved by warming a suspension of potassium-β-methylcinnamate in dichloromethane with oxalyl chloride until no further evolution of gas was observed. The resulting solution was then used to acylate harmalan in the usual way and, after chromatography on alumina, the dienamide [(254), R = CH_3] was obtained in 66% yield.

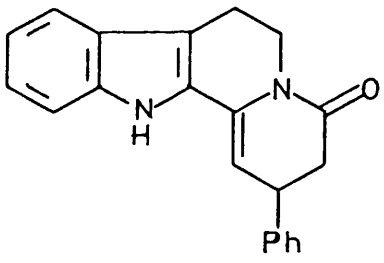


Scheme 61

Irradiation of a methanolic solution of the dienamide with 365 nm u.v. light did not lead to cyclised product even after prolonged reaction times. A thermal ring closure was attempted by heating the dienamide at 200° C for thirty minutes but again, cyclisation did not take place. This lack of reactivity was surprising and not easily explained and so to provide further information about the reactivity of the cinnamoyl derivatives of harmalan, the unsubstituted dienamide [(254), R = H] was prepared.

The synthesis of this derivative was achieved in 72% yield by treating harmalan with cinnamoyl chloride in the presence of triethylamine. The ^1H n.m.r. of the dieneamide was noteworthy by virtue of the fact that the resonances of the exocyclic methylene protons appeared as two singlets at δ 4.96 and δ 5.78, rather than the double doublet expected. The coupling constant of geminally coupled alkene hydrogens is generally of the order 3-7 Hz, although in the case of the indole-2-carbonyldienamide [(233), R = CH_3] described previously, a coupling constant of approximately 2 Hz was observed.

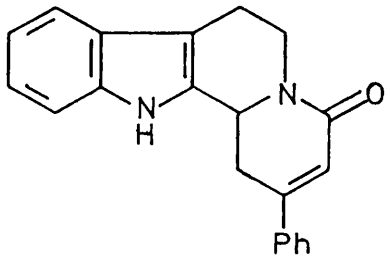
A methanolic solution of the dienamide [(254), R = H] was subjected to pyrex filtered u.v. irradiation at 365 nm for twenty-four hours and this time cyclisation did take place. After work-up, a 75% yield of the X-type migration product (258) was obtained. In



(258)

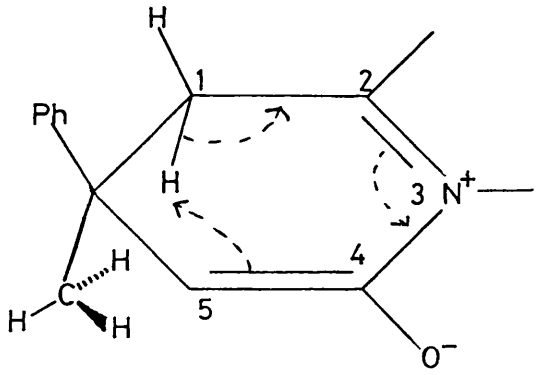
contrast to the cyclisation of the indolic dienamides [(233), R = CH_3] and [(235), R = CH_5], the cyclised cinnamoyl derivative (258) showed no inclination to aromatise.

Although precedented,[90] the formation of the X-type migration product (258), rather than the Z-type migration product (259), was nevertheless a disappointment to us since it rendered invalid our intended scheme to synthesise novel bridged indole ring systems of the type (263) referred to previously.



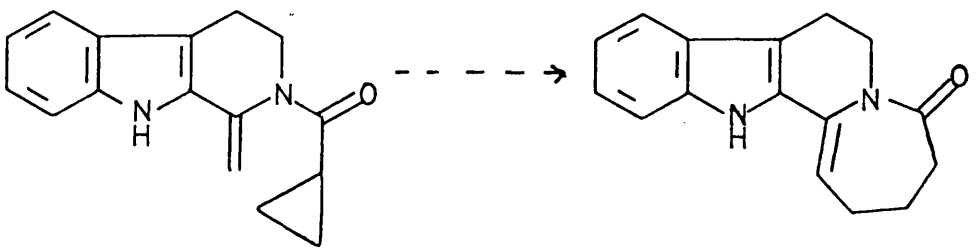
(259)

However, the fact that the unsubstituted cinnamoyl-dienamide underwent cyclisation, whereas the β-methyl substituted derivative did not, was interesting, and a possible explanation is that initial cyclisation does occur, but the methyl group sterically hinders the sigmatropic transfer of the hydrogen atom from the 1- position to the 5- position in the presumed transition state (260).



(260)

Finally, the possibility of synthesising azepinone-fused β-carbolines was investigated (see Scheme 62). The cyclopropylenamide (261) was therefore prepared in 58% yield by acylating harmalan with



(261) (262)

Scheme 62

cyclopropylcarbonyl chloride and chromatographing the crude product on silica.

The cyclopropylenamide was irradiated with a medium pressure u.v. lamp in methanol solution, but although t.l.c. analysis showed that starting material was being consumed, no major product formation was observed. Instead, it appears that complex breakdown was taking place and further analysis of the reaction mixture proved fruitless. It is possible that the use of different photochemical conditions, *e.g.*, different solvents, sensitisers and more careful control of the u.v. wqvelengths used, may result in cyclisation. Alternatively, a thermal cyclisation is also feasible. However, lack of time precluded investigations and this route was therefore reluctantly abandoned.

CHAPTER 6

E X P E R I M E N T A L

General Procedures

Unless otherwise stated, ultraviolet spectra were recorded as solutions in 98% ethanol and infra-red spectroscopic data refer to Nujol mulls.

^{1}H N.m.r. spectra were recorded at 90, 100 and 250 MHz, using tetramethylsilane as an internal standard.

Flash chromatography refers to the technique devised by Still.[144] The column was pressurised using nitrogen so as to prevent oxidation of the substances being chromatographed.

Tetrahydrofuran (referred to as THF in the text) was dried by distillation from either calcium hydride or sodium benzophenone ketyl. Dichloromethane was distilled from phosphorus pentoxide.

The drying of solutions before evaporation was accomplished using magnesium sulphate unless otherwise stated.

Photolyses were carried out with either a 125 W or a 400 W medium pressure u.v. lamp, using a quartz immersion well.

1-Phenylsulphonylindole (208).-Finely powdered potassium hydroxide (22.5 g) was added to dry dimethylsulphoxide (200 cm^3) under an atmosphere of dry nitrogen and the mixture was stirred at room temperature until most of the solid had dissolved. Indole (11.7 g) was then added and the mixture was stirred at ambient temperature for 3 h, followed by 45 min at 50° C before cooling in an ice-bath. Phenylsulphonyl chloride (35g, 25.3 cm^3) was added dropwise, so that the temperature did not exceed 20° C, and when addition was complete the solution was stirred for a further 30 min before the careful addition of water (125 cm^3). Addition of a further volume (300 cm^3) of water gave rise to an oily precipitate, which solidified on being scratched. The solid was filtered off, sucked dry and recrystallised twice from methanol. After drying *in vacuo* at 30-40° C, the yield of 1-phenylsulphonylindole was 17.6 g (68.5%). M.p. (methanol) = 76-78° C (lit.,[113] 77.5-79° C). ^1H n.m.r. $\delta(CDCl_3)$: 7.75-8.1 (3H, m, aromatics), 7.0-7.6 (7H, m, aromatics), 6.6 [1H, d, (J = 8 Hz), indole H-3]; ν_{max} (cm^{-1}): 3140, 3060, 1440, 1370, 1260, 1170, 1130, 1088, 725; λ_{max} (nm): 212, 247, 289(sh).

1-Phenylsulphonyl-2-trimethylsilylindole (210).-*N*-Phenylsulphonylindole (8.34 g, 0.328 mol) was dissolved in freshly dried and distilled THF (100 cm^3) under a nitrogen atmosphere. The solution was cooled to -78° C and a solution of 1.64 *M* *n*-butyllithium in hexane (20 cm^3, 0.0328 mol) was added. After allowing to warm to approximately 0° C (30 min) the mixture was again cooled to -78° C and excess trimethylsilyl chloride was added. The cold bath was removed and the solution was allowed to warm to room temperature before removal of the solvent under reduced pressure. The residue was partitioned between brine and ether, the organic layer separated and the aqueous phase washed once more with ether. The combined ether layers were dried over magnesium sulphate and evaporated down to give a pale-yellow oil. Chromatographic analysis (20% ethylacetate in petrol/silica) revealed the title compound (Rf 0.6) to be the major component of the oil with a small amount of

starting material (Rf 0.5) remaining. The oil was adsorbed onto silica and subjected to flash chromatographv using 5% ethylacetate in petrol as the eluent. Collection and evaporation of the product fractions yielded 1-phenylsulphonyl-2-trimethylsilylindole as a colourless oil which slowly crystallised. Yield = 6.56 g (61%); m.p. (60-80° petrol) = 75-76° C. ^{1}H n.m.r. $\delta(CDCl_3)$: 7.2-8.1 (9H, H-4, 5, 6 and 7 and phenyl protons), 7.05 (1H, s, indole H-3), 0.57 (9H, s, SiMe); ν_{max} (cm^{-1}): 1363, 1175, 850. [Found: C, 61.95; H, 5.98; N, 4.15. $C_{17}H_{19}NO_2SSi$ requires: C, 61.97; H, 5.81; N, 4.25%]; λ_{max} (nm): 214, 255, 285(sh).

Reaction of 2-lithio-1-phenylsulphonylindole with electrophiles.-Phenylsulphonylindole was lithiated according to the procedure described for the synthesis of 1-phenylsulphonyl-2-trimethylsilylindole.

Reaction with mesitylenesulphonylhydroxylamine (MSH).-To a solution of the lithioindole (2.3 mmol) at -78° C, was added a solution of MSH* (0.5 g, 2.3 mmol) in THF which had previously been stored over 4 Å molecular sieves for 90 min in order to remove the water of crystallisation from the reagent. An immediate reaction took place with the vigorous evolution of gas, formation of a brown colour in the solution and fuming all being observed. Partition of a small sample between water and ethylacetate and subsequent t.l.c. analysis (10% ethylacetate in petrol/silica) of both phases showed only *N*-phenylsulphonylindole (Rf 0.15) with traces of brown baseline impurity. Further chromatographic analysis (silica/10% methanol in dichloromethane) similarly showed starting material (Rf 0.9) to be the only major component.

Reaction with nitrosonium tetrafluoroborate.-To a solution of 2-lithio-1-phenylsulphonylindole (1.5 mmol) in THF at -78° C was added nitrosonium tetrafluoroborate (0.175 g, 4.5 mmol) under a strong current of dry nitrogen. Stirring was maintained at -78° C

*MSH prepared according to the procedure of Johnson (see Chapter 3).

for 2 h, during which time no reaction took place, and the solution was then allowed to come to room temperature overnight. T.l.c. analysis (10% ethylacetate in petrol/silicon) showed starting material to be the sole major component, although traces of minor decomposition products were discernable. A minor product appearing as a streak between the baseline and Rf 0.2 did not react with potassium permanganate or acidified iodoplatinate spray reagents. Further analysis was unproductive.

Reaction with isoamylnitrite.-Dry redistilled isoamylnitrite (2 cm^3) was added to a solution of the lithiated indole (4.8 mmol) in THF at -78° C. A cherry-red colour developed very quickly, but t.l.c. analysis showed only starting material. The mixture was allowed to warm to room temperature, whereupon formation of a black colouration was observed. Again t.l.c. analysis showed that no products had been formed. After prolonged stirring at room temperature the solution was evaporated down and *N*-phenylsulphonyl recovered by extraction into ether. The identity of the starting material was confirmed by n.m.r. analysis.

Reaction with nitronium tetrafluoroborate.-Nitronium tetrafluoroborate (0.412 g, 3.1 mmol) was added to a solution of 2-lithio-1-phenylsulphonylindole (3.1 mmol) in THF at -78° C. The nitronium salt dissolved very slowly, solution being accompanied by the formation of a yellow colour. After stirring for 1 h at -78° C. t.l.c. analysis showed that only starting material was present and therefore the solution was allowed to come to room temperature overnight, during which time the salt completely dissolved. Again no products were observed and so *N*-phenylsulphonylindole was recovered in the usual way.

Reaction with 1-azido-1-phenylethene.-To a cold (-78° C) solution of the lithiated indole (1.28 mmol), 1-azido-1-phenylethene (125 mg, 1.28 mmol) in petrol was added and the solution was allowed to come to room temperature. After 2 h, t.l.c. analysis indicated the formation of a small amount of product, although starting material formed the major part of the mixture. Further stirring at room temperature did not result in additional reaction and so the solution was treated with an aqueous solution of potassium hydroxide (0.5 g).

After stirring for 30 min the mixture was acidified and extracted with ethylacetate. Analysis of the organic phase showed starting material and a number of minor products which were not identified. The aqueous phase was basified and re-extracted with ethylacetate. No compounds were found in the organic layer indicating that 2-amino-1-phenylsulphonylindole had not been formed.

1-Azido-1-phenyl-2-iodoethane.-Sodium azide (17.5 g) was added to dry redistilled acetonitrile (120 cm^3) and the mixture was cooled in a methanol/ice bath to -20° C. Iodine monochloride* (6.7 cm^3, 21.3 g) was introduced dropwise over 20 min and to the resulting canary-yellow suspension was added redistilled styrene (13.3 cm^3, 12.1 g). The cool bath was removed and the mixture was stirred for 22 h before pouring into water (280 cm^3). After extracting with ether (3 x 50 cm^3) the reddish organic phase was washed with 5% sodium thiosulphate (150 cm^3) and then water (4 x 200 cm^3) before drying over magnesium sulphate and evaporating down under reduced pressure. Thin layer chromatographic analysis (alumina/petrol) of the residual yellow liquid (18.53 g, 58%) showed only one spot (Rf 0.4) due to the title compound. ^1H n.m.r. $\delta(CDCl_3)$: 7.3 (5H, s, aromatics), 4.72 [1H, t, (J = 14 Hz)$_{Ph}^{N_3}$ $\underline{CH}$], 3.38 [2H, d, (J = 14 Hz), $-CH_2-$]; ν_{max} (cm^{-1}): 2130, 1250, 700; λ_{max} (nm): 216, 251, 257(sh).

1-Azido-1-phenylethene(228).-1-Azido-1-phenyl-2-iodothane (17.6 g) was dissolved in dry ether (250 cm^3) under an atmosphere of nitrogen. Potassium *t*-butoxide (8.7 g) was added, resulting in the rapid evolution of gas and darkening of the solution. When the initial reaction had subsided, the solution was stirred for 1 h at room temperature, after which time t.l.c. analysis (alumina/petrol) showed the presence of one major product (Rf 0.7) with no starting material remaining. The solution was poured into water; the ether layer being removed and washed three times with water before drying over magnesium sulphate and evaporating down to a brown oil. The crude

*Iodine monochloride is solid at room temperature, but may be melted and maintained in the molten state using a hair dryer.

product was purified by chromatography on alumina using petrol as the eluent. Evaporation of the product fractions yielded the title compound as a colourless oil (4.9 g, 52%). ^{1}H n.m.r. $\delta(CDCl_3)$: 7.2-7.8 (5H, m, aromatics, 5.5 [1H, d, (J = 5 Hz), E—alkenic proton], 4.93 [1H, d, (J = 5 Hz), Z-alkenic proton]; ν_{max} (liquid film) (cm^{-1}): 2120, 2145, 2200.

The reaction of 1-phenylsulphonyl-2-trimethylsilylindole with electrophiles.-With mesitylenesulphonylhydroxylamine (MSH). MSH (137 mg, 0.6 mmol) was added to a cold solution of the silyl compound and the resulting mixture stirred at ambient temperature for 20 h. T.l.c. analysis (20% ethylacetate in petrol/silica) after this time showed that no reaction had occurred. The solution was not heated because of the known explosive nature of MSH.

With MSH and catalytic potassium-t-butoxide.-1-Phenylsulphonyl-trimethylsilylindole (0.5 g, 1.5 mmol) and MSH (0.36 g, 1.65 mmol) were dissolved in DMF (10 cm^3) and potassium t-butoxide (10 mg) added. The solution rapidly acquired a reddish colour, but t.l.c. analysis (10% ethylacetate in petrol/silica) showed no products. It seems likely that breakdown of the reagent had occurred.

With nitrosonium tetrafluoroborate.-The silyl-indole (0.53 g, 1.6 mmol) was dissolved in sulpholane (10 cm^3, distilled under reduced pressure from calcium hydride) at 30° C and nitrosonium tetrafluoroborate (183 mg, 1.6 mmol) was added under a strong current of nitrogen. The solution, which was stirred at 30° C, rapidly acquired a reddish colour. After 4 h, all starting material had been consumed and so the solution was poured into water and extracted with ethylacetate. The organic phase was extracted with brine (3 x 100 cm^3) to remove any sulpholane, dried with sodium sulphate and evaporated down under reduced pressure to yield a red oil. T.l.c. analysis on silica using 10% ethylacetate in petrol as the eluent showed only red baseline material. Increasing the polarity of the solvent did not lead to any resolution of the product. ^{1}H n.m.r. analysis of the crude material was likewise fruitless.

With isoamylnitrite (i).-The silyl indole (1.4 mmol) and isoamylnitrite (a slight excess) were dissolved in benzene and boiled for 22 h. T.l.c. analysis (10% ethylacetate in petrol/silica) after this time indicated that no reaction had taken place.

With isoamylnitrite (ii).-1-Phenylsulphonyl-2-trimethylsilylindole (1.9 mmol) was dissolved in dry isoamylnitrite and the reaction mixture was placed under a positive pressure of nitrogen before boiling for 32 h. A trace of 1-phenylsulphonylindole was present after this time, but no other products were observed. Further boiling for 63 h (during which time the protective nitrogen atmosphere was lost) resulted in formation of a substantial quantity of the desilylated product, which was isolated and characterised by ^{1}H n.m.r. No nitrosation prdoucts were detected.

With nitronium tetrafluoroborate.-1-Phenylsulphonyl-2-trimethylsilylindole (1.28 g, 3.9 mmol) was dissolved in dry dichloromethane (15 cm^3) under an atmosphere of nitrogen and the solution was cooled to -76° C. Nitronium tetrafluoroborate (0.52 g, 3.92 mmol) was added under a stream of nitrogen and the mixture stirred in the cold for 1 h. During this time, small samples were taken, partitioned between ethylacetate and sodium carbonate solution and subjected to t.l.c. analysis (30% ethylacetate in petrol/silica). No reaction was observed at -76° C, therefore the solution was gradually allowed to warm to 0° C, whereupon formation of a product took place. After 2 h at 0° C, the reaction had reached a standstill and so the solution was poured into 2 *M* sodium carbonate and extracted with ethylacetate. The organic phase was dried and evaporated down to a brown gummy residue, t.l.c. analysis of which revealed the presence of a considerable amount of *N*-phenylsulphonylindole, a small amount of starting material and a low concentration of a product. The residue was then subjected to flash chromatography on silica (5% ethylacetate in petrol) with 7 cm^3 fractions being taken. Fractions 28-30 afforded a small quantity of a product, contaminated with *N*-phenylsulphonylindole, which was analysed by mass spectrometry; m/e E.I. 12 eV (%): 374 ($C_{17}H_{18}N_2O_4SSi$, 11), 359 (72), 302 (6), 257 (100), 234 (50), 219 (28), 116 (50). Insufficient material was available for further analysis.

The mixed fractions 36-51 were rechromatographed to yield 250 mg (25%) of pure *N*-phenylsulphonylindole, the identity of which was confirmed from the n.m.r., i.r. and mass spectral data. Further examination of the mixed fractions proved fruitless with gradual decomposition of the nitrated product taking place with each successive manipulation.

With benzaldehyde.-The silylindole was dissolved in an excess of benzaldehyde and the solution was brought to reflux. After boiling under a nitrogen atmosphere for 15 h, t.l.c. analysis showed only starting materials and benzaldehyde decomposition products.

With bromine.-The silyl compound (1 g) was dissolved in carbon tetrachloride and to the cooled solution was added bromine (0.08 cm^3, 1 equivalent). The mixture was stirred at 0° C for 90 min, the progress of the reaction being monitored by t.l.c. (silica/5% ethylacetate in petrol). After pouring into saturated sodium bicarbonate solution, the organic phase was separated, dried and evaporated down. The residue was refined twice by flash chromatography on silica, using 2% ethylacetate in petrol as the eluent, to yield *N*-phenylsulphonylindole (234 mg, 30%) and a mixture of desilylated monobromo- and dibromo-*N*-phenylsulphonylindoles (175 mg, ∿15%). Several recrystallisations from petrol were carried out but further separation was not achieved. The product was chromatographically homogeneous and possessed a sharp melting point, but ^1H n.m.r. and i.r. spectral data indicated it to be a mixture; m/e: 425, 336, 284, 195, 141, 77, m.p. = 101.5-103° C.

The reaction of 1-phenylsulphonyl-2-trimethylsilyldinole with nucleophiles.-With tetra-n-*butylammonium fluoride*. The silylindole (133 mg, 0.4 mmol) was dissolved in dry THF and tetra-*n*-butylammonium fluoride (370 mg, 0.4 mmol) was added. The solution was stirred under nitrogen at room temperature for 75 min, by which time all starting material had been consumed. The mixture was poured into water and extracted with ether (2 x 100 cm^3); the organic phase was subsequently removed, dried and evaporated down to yield a colourless oil. Recrystallisation from methanol afforded

N-phenylsulphonylindole as the sole product, comparable by m.p. (77° C), t.l.c. (Rf 0.15 on silica/10% ethylacetate in petrol) and ^{1}H n.m.r. with a genuine sample.

With sodium methoxide.-Sodium (42 mg) was added to dry ether under a current of nitrogen. Methanol (1 cm^3) was then added and the mixture was stirred until the sodium had dissolved. A solution of 1-phenylsulphonyl-2-trimethylsilylindole (590 mg) in dry ether was subsequently introduced and the resulting mixture was stirred for 1 h. T.l.c. analysis (10% ethylacetate in petrol) showed that no reaction had taken place and so the solution was warmed until gentle refluxing was achieved. After a further hour, analysis revealed that desilylation was occurring to give 1-phenylsulphonylindole (Rf 0.15). Prolonged heating led to an increase in the concentration of the desilylated product, although a considerable quantity of the starting material (Rf 0.3) remained. Evaporation of the solvent, extraction into ether and removal of the solvent from the organic phase yielded an oil which was recrystallised from methanol to afford 1-phenylsulphonylindole. The identity of the product was confirmed by the m.p. and by ^{1}H nm..r. spectroscopic analysis.

With diethylamine.-The silyl compound (100 mg) and diethylamine (2 cm^3) were dissolved in benzene (8 cm^3) and the solution was stirred at room temperature for 17 h, during which time no reaction was observed. The mixture was then heated at reflux for a further 6 h, after which t.l.c. analysis again showed that no reaction had taken place.

With sodium diethylmalonate.-Sodium hydride (100 mg, 4 mmol) was added to a solution of redistilled diethylmalonate (0.5 cm^3, 3.3 mmol) in freshly dried and distilled THF (12 cm^3). The suspension was stirred at room temperature under an atmosphere of nitrogen until evolution of gas had ceased (30 min). The trimethylsilylindole (1.084 g, 3.3 mmol) was then added and the solution was stirred at ambient temperature for 16 h, during which time partial desilylation

was observed. This process was brought to completion by boiling the solution for 4 h. The cooled solution was evaporated down and the residue was partitioned between water and ethylacetate. The organic layer was dried and evaporated down under reduced pressure to give an oil which slowly crystallised. T.l.c. analysis (30% ethylacetate in petrol/silica) showed the presence of a trace of starting material and a predominance of *N*-phenylsulphonylindole. Recrystallisation of the product from methanol yielded pure *N*-phenylsulphonylindole (0.51 g, 60%), which was identical (t.l.c., m.p., i.r.) with a genuine sample.

2-Aminophenylacetonitrile.-A suspension of 2-nitrophenylacetonitrile (10 g) in absolute ethanol (100 cm^3) was cooled to -15° C. Tin foil pieces (12.5 g) and concentrated hydrochloric acid (56 cm^3) were then added in alternate portions over 45 min, care being taken to ensure that the temperature did not rise above -5° C. When addition was complete, the mixture was stirred for a further 5 min. before removal of the cold bath. The resulting pale-orange solution was stirred at room temperature overnight. Evaporation to minimal volume under reduced pressure using a 'cold finger' attachment gave rise to precipitation of a tin double salt (14.44 g), which was filtered off, washed with ethanol and air dried. The salt was taken up in water (180 cm^3) and to the cooled and filtered solution was added, dropwise over 30 min, 30% sodium hydroxide (26 cm^3). Vigorous stirring was required to prevent the mixture becoming too viscous. When addition was complete, the suspension was set aside on ice for a further 15 min before filtering. After washing sparingly with cold water and partially air drying, the product was freeze dried overnight to give the title compound as a colourless solid (6.1 g, 75%), which acquired a purple colouration on prolonged exposure to air. ^1H n.m.r. $\delta(CDCl_3)$: 6.6-7.4 (4H, m, aromatics), 3.7 (2H, bs, disappears when D_2O added, NH_2), 3.5 (2H, s, $-CH_2-$); ν_{max} (cm^{-1}): 3430, 3360, 2260, 1640, 1465, 763.

2-Aminoindole.-To freshly dried, distilled and deoxygenated absolute ethanol (25 cm^3) was added freshly cut sodium (0.94 g). When the sodium had completely dissolved, 2-aminobenzylcyanide (1.5 g) was added and the mixture was brought to reflux. After boiling under an atmosphere of nitrogen for 30 min, the solution was cooled to room temperature and deoxygenated water (25 cm^3) was added. Slow evaporation of the solution under reduced pressure resulted in the appearance of a lustrous crystalline precipitate which was filtered off under nitrogen and dried *in vacuo*. The filtrate was chilled in a refrigerator overnight to yield a further crop of product. Total yield = 0.83 g (55%): ^1H n.m.r. $\delta(d^4\text{-}CH_3OH)$: 7.23 [1H, d, ($J$ = 8 Hz), H-4], 7.14 [1H, t, (J = 8 Hz), H-6], 7.00 [1H, d, (J = 8 Hz), H-7], 6.88 [1H, t, (J = 8 Hz), H-5]; m/e E.I. 12 eV: 132 (M^+); ν_{max} (cm^{-1}): 3310, 1660, 1520, 760; λ_{max} (nm): 259(sh), 267, 276(sh), 349.

N.B. 2-Aminoindole is extremely susceptible to aerial oxidation, particularly when in solution and so manipulations were carried out using deoxygenated solutions under a nitrogen atmosphere wherever possible.

2-Benzamidoindole.-A solution of 2-aminoindole (0.57 g, 4.3 mmol) in dry deoxygenated pyridine (15 cm^3) was cooled on an ice bath and 4-dimethylaminopyridine (52.5 mg, 0.43 mmol) was added. Benzoyl-chloride (0.5 cm^3, 4.3 mmol) was then introduced dropwise with care. When addition was complete, the solution was stirred at room temperature for 1 h before partitioning between ethylacetate (100 cm^3) and 2 *M* hydrochloric acid (100 cm^3). The organic phase was washed again with hydrochloric acid (100 cm^3) and then saturated brine (100 cm^3) before drying and evaporating down in the presence of silica. The silica-adsorbed crude product was applied to the top of a 6 cm^3 diameter silica column and subjected to flash chromatography using 15% ethylacetate in petrol as the eluent. The first 60 cm^3 of eluent were run to waste and thereafter 20 cm^3 fractions were taken. Fractions 21-40 were combined, filtered and evaporated to yield a pale-green crystalline substance which was identified as 1-benzoyl-2-benzamidoindole (200 mg, 14%). Fractions 61-81 were similarly

combined and evaporated to yield the title compound 2-benzamidoindole (360 mg, 35%); m.p. 187-189° C. ^{1}H n.m.r. δ($CDCl_3$-d^6-DMSO): 10.55 (2H, bs, N-H and N'-H), 8.01 (2H, m, *ortho*-benzoyl protons), 7.0-7.6 (7H, m, indole H-4, 5, 6 and 7, and benzoyl H-3', 4' and 5'), 6.28 [1H, dd, (J = 3 Hz), (J = 1 Hz), H-3];* m/e E.I. 12 eV (%): 236 (M^+, 100), 105 (68), 77 (45), 51 (41); ν_{max} (cm^{-1}): 3430, 3320, 1650, 1540; [Found: C, 76.33; H, 5.10; N, 11.63. $C_{15}H_{12}N_2O$ requires: C, 76.25; H, 5.12; N, 11.86%].

Data for 1-benzoyl-2-benzamidoindole.-M.p. 141.5-144° C. ^{1}H n.m.r. δ($CDCl_3$): 11.30 (1H, s, N'-H), 8.00, 7.65-7.8 and 7.36-7.6 (11H, 3 x m, phenyl ring protons and indole H-4), 7.44 (1H, s, H-3), 7.16 and 6.87 [2 x 1H, 2 x t, (J = 8 Hz), H-5 and H-6], 6.33 [1H, d, (J = 8Hz), H-7]; m/e E.I. 13 eV (%): 340 (M^+, 11), 105 (100), 77 (44); ν_{max} (cm^{-1}): 3290, 1680, 1670, 745, 730, 710, 700; [Found: C, 77.27; H, 4.82; N, 8.04. $C_{22}H_{16}N_2O_2$ requires: C, 77.63; H, 4.74; N, 8.23%]; λ_{max} (nm): 209, 234, 310.

The photochemistry of 2-benzamidoindole.-Irradiation under anaerobic conditions. 2-Benzamidoindole (300 mg) was dissolved in analar grade methanol (500 cm^3) and the solution was flushed with nitrogen for 30 min before irradiating for 18 h with a medium pressure 400 W u.v. lamp fitted with a quartz sleeve. A nitrogen atmosphere was maintained throughout the period of irradiation. T.l.c. and u.v. analysis of the reaction mixture after 18 h indicated that cyclisation was not taking place.

Irradiation under oxidising conditions.-A solution of 2-benzamidoindole (110 mg) in analar grade benzene (150 cm^3) was irradiated with a 400 V medium pressure u.v. lamp for 16½ h at room temperature. T.l.c. (30% ethylacetate in petrol /silica) and u.v. analysis during this time indicated that cyclisation was not taking place, although the appearance of decomposition products was noted. Iodine was added and the solution was irradiated for a further 4 h. Product formation was observed immediately after the addition of the oxidant, but little change was observed during the remaining photolysis period.

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*No coupling is observed when D_2O is added to the solution.

Comparison of the reaction mixture with a control solution of 2-benzamidoindole treated with iodine demonstrated that the reaction products had arisen purely as a result of the presence of the iodine and not through any photochemical process.

The photochemistry of 2-benzamido-1-benzoylindole.-A solution of 2-benzamido-1-benzoylindole (53 mg) in methanol (75 cm^3) was subjected to irradiation with a 125 W medium pressure lamp contained in a quartz immersion well. T.l.c. analysis (30% ethylacetate in petrol/silica) demonstrated that gradual *N*-debenzoylation was taking place to yield 2-benzamidoindole with subsequent slow decomposition of the mono-benzoyl derivative. After a total of 84 h of irradiation it was apparent that no cyclisation was taking place, ahtough by this time, little starting material remained. The nummerous spots visible on the t.l.c. plate indicated that general breakdown was occurring. No one component was present in sufficiently high concentration to enable characterisation to be attempted.

2-Benzaliminoindole.-A mixture of 2-aminoindole (562 mg, 4.26 mmol) and freshly distilled benzaldehyde (0.5 cm^3, 4.9 mmol) in dry de-oxygenated benzene (10 cm^3) was stirred at room temperature for 45 min. The resulting precipitate was filtered off under nitrogen and dried under vacuum to yield the title compound as an off-white solid (0.61 g, 65%). ^1H n.m.r. $\delta[d^6$-DMSO/$(CD_3)_2CO]$: 10.3 (1H, bs, N-H), 7.0-8.0 (10 H, m, indole H-4, H-5, H-6, H-7, phenyl protons, imine α-hydrogen), 6.25 (1H, s, H-3); m/e E.I. 12 eV (%): 220 (M^+); ν_{max} (cm^{-1}): 3380, 1635, 1568, 1492, 1015. The compound was insufficiently stable for further analysis to be carried out.

The photochemistry of 2-benzalaminoindole.-The imine (200 mg) was partially dissolved in dry deoxygenated benzene (400 cm^3) and the resulting mixture was irradiated overnight with a 125 W medium pressure u.v. lamp. Nitrogen was bubbled through the solution during the entire period of rraidation. U.v. analysis after this period showed no change. Similar experiments carried out in the presence of limonene or nitrobenzene also failed to result in cyclisation. Irradiation of a solution of the imine with a 16 W low pressure lamp for a total of 64 h caused extensive decomposition, but no α-carboline formation was observed.

N-Acetyltryptamine.-Tryptamine (10.5 g) was dissolved in 95% ethanol (100 cm^3) and acetic anhydride (25 cm^3) was added. The solution was stirred at room temperature for 15 min before evaporating down to minimum volume under reduced pressure at 20° C. The residue was partitioned between dichloromethane and water and the two phase mixture thoroughly emulsified before solid sodium carbonate was added to destroy the excess reagent. After stirring vigorously for 2 h the organic layer was separated, dried and evaporated down to give an oil which slowly crystallised. Yield = 12.6 g (94%): m.p. (ether/petrol) = 76-77° C (lit.,[145] 77° C). ^{1}H n.m.r. $\delta(CDCl_3)$: 8.7 (1H, bs, indole N-H), 7.55 [1H, dd, (J = 8 Hz), (J = 1Hz), H-4], 6.9-7.4 (3H, m, H-5, H-6, H-7), 6.94 [1H, d, (J = 1 Hz), H-2],* 5.77 (1H, bs, NH-Ac), 3.55 [2H, q, (J = 6Hz), CH_2-N],† 2.94 [2H, t, (J = 6 Hz), -CH_2-], 1.87 (3H, s, $COCH_3$); ν_{max} (cm^{-1}): 3405, 3265, 3080, 1630, 1560, 745; λ_{max} (nm): 231, 274(sh), 282, 291(sh).

1-Methyl-3,4-dihydro-β-carboline (harmalan) (153).-*N*-Acetyltryptamine (3 g, 0.015 mmol) was dissolved in warm dry xylene (200 cm^3) under an atmosphere of dry nitrogen. Phosphorus pentoxide (37.5 g) was added in three portions over 30 min, and the resulting suspension was stirred vigorously for 45 min before being brought to reflux. After boiling for 90 min, the mixture was allowed to cool to room temperature whereupon the xylene was decanted off and the residual red slurry washed several times with petrol to remove any traces of the higher boiling solvent. The residue was poured carefully onto ice and the mixture was allowed to come to room temperature before the addition of 2 *M* hydrochloric acid (7.5 cm^3). The reddish solution was subsequently washed several times with petrol and then basified with sodium carbonate. Extraction with ether (2 x 200 cm^3), drying of the extracts over magnesium sulphate and evaporation afforded the title compound as a yellow solid (1.25 g). The aqueous layer was made strongly alkaline with sodium hydroxide and extracted again with ether (2 x 200 cm^3). In this way a further crop (0.6 g)

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*Collapsed to singlet when resonance at δ 8.7 irradiated.

†Collapsed to triplet upon irradiation of signal at δ 5.77.

of product was obtained. Total yield = 1.85 g (68%): m.p. = 182.5-185° C (lit.,[124] 183-185° C). ^{1}H n.m.r. δ($CDCl_3$): 10.32 (1H, bs, N-H), 7.61 [1H, dd, (J = 7 Hz), (J = 1 Hz), H-4], 7.0-7.5 (3H, m, H-5, H-6 and H-7), 3.93 [2H, t, (J = 9 Hz), $-CH_2-N$], 2.89 [2H, t, (J = 9 Hz), $-CH_2-$], 2.4 (3H, s, CH_3); m/e E.I. 12 eV %: 184; ν_{max} (cm^{-1}): 1602, 1550, 738; λ_{max} (nm): 242, 315, 345(sh).

Ethyl indole-2-carboxylate (240).-Dry ether (100 cm^3) was placed in a two litre, three-necked flask fitted with a dropping funnel, mechanical stirrer and a reflux condenser. Under a current of dry nitrogen, freshly cut potassium pieces (11.2 g) were added, followed by a mixture of absolute ethanol (70 cm^3) and dry ether (60 cm^3) which was added at such a rate as to maintain gentle refluxing. When the potassium had completely dissolved, the solution was allowed to cool before the addition of a further quantity (700 cm^3) of ether. This was followed by the addition of diethyl oxalate (41.7 g, 38.6 cm^3) and, after another 10 min, 1-nitrotoluene (39.1 g). The mixture was stirred for 10 min and then poured into a two litre conical flask which was tightly stoppered and set aside for 48 h. The resulting lumpy deep-purple potassium salt of ethyl-2-nitrophenylpyruvate was filtered off, washed well with ether and air dried. Yield = 59 g (74%).

Potassium ethyl-2-nitrophenylpyruvate (29 g) was dissolved in glacial acetic acid (200 cm^3) and hydrogenated at 30 p.s.i. for 7½ h. over 5% palladium on charcoal catalyst. The hydrogenation mixture was filtered to remove the catalyst and then poured into water (100 cm) to precipitate the product ester as a pale-yellow solid (8.3 g, 42%) which was filtered, washed well with water and air dried. The crude ester (6.23 g) was dissolved in dichloromethane and filtered through a bed of alumina to remove any residual catalyst and traces of the unreduced nitro compound. After evaporation of the solvent, the residue (5.77 g) was recrystallised from dichloromethane/petrol to yield the pure product as glistening colourless needles (3.5 g), m.p. 123-124° C (lit.,[133] 118-124° C). ^{1}H n.m.r. δ($CDCl_3$): 9.2 (1H, bs, N-H), 7.72 [1H, d, (J = 7 Hz), H-4], 7.05-7.75 (4H, m, H-3, H-5, H-6 and H-7), 4.43 [2H, q, (J = 7 Hz), $-CH_2-$],

1.45 [3H, t, (J = 7 Hz), $-CH_3$]; ν_{max} (cm^{-1}): 3320, 1690, 1520, 1250, 1200, 1020, 820.

Indole-2-carboxylic acid.-Ethyl indole-2-carboxylate (2 g) was suspended in 1 *M* sodium hydroxide (26 cm^3) and the mixture was heated at 83° C on a water bath for 90 min. After cooling, the solution was filtered and acidified to give the title compound as a white flocculent precipitate which was filtered off, washed well with water and dried in a vacuum dessicator over phosphorus pentoxide. Yield = 1.46 g (86%): m.p. (ether/petrol) = 206-207° C (lit.,[146] 205-208° C). ^1H n.m.r. $\delta(d^6$-DMSO): 12.8 (1H, bs, CO H), 11.8 (1H, bs, N-H), 7-7.9 (5H, m, aromatics); m/e E.I. 70 eV (%): 161 (M^+), 143, 115, 89, metastables at 127 (161 → 143) and 92.5 (143 → 115); ν_{max} (cm^{-1}): 3350, 1710, 1620, 1515, 1436, 1180, 820, 770, 730.

Indole-2-carboxylic acid chloride.-The following methods were used to prepare indole-2-carbonyl chloride.

Method 1

Indole-2-carboxylic acid (0.17 g) was dissolved in dry ether (10 cm^3) and freshly redistilled thionyl chloride (0.75 cm^3) was added. The yellow solution was allowed to stand for 1 h before evaporating down to a yellow solid. Ether was added and the solution was re-evaporated to remove traces of thionyl chloride. The canary-yellow acid chloride was kept under nitrogen until required. M.p. = 102-109° C (lit.,[135] 107-112° C). M/e E.I. eV (%): 181,179 (M^+), 161 (starting material impurity). The anilide of the acid was formed by treatment of the acid chloride with excess aniline in ether. After removal of the solvent the residue was treated with 2 *M* hydrochloric acid; the resultant colourless precipitate being filtered off, washed well with water and then recrystallised from methanol. M.p. = 170-171° C (lit.,[150] 170-170.5° C). M/e E.I. eV (%): 236 (base peak - M^+).

Method 2

Indole-2-carboxylic acid (2 g) was dissolved in aqueous acetone and to the resultihng solution was added powdered sodium hydroxide. The mixture was stirred for 20 min and then evaporated down under

reduced pressure. The residual salt was dried in high vacuum.

Sodium indole-2-carboxylate (42 mg, 0.23 mmol) was suspended in dry benzene (5 cm^3) and oxalyl chloride (0.02 cm^3, 0.3 mmol) added. The suspension was warmed on a water bath (≈ 40° C) to initiate reaction and was maintained at this temperature until evolution of gas had ceased. At this point, formation of the acid chloride was judged to be complete.

Attempted acylation of harmalan.-The acid chloride solution described above was added dropwise to a solution of harmalan (42 mg, 0.3 mmol) in dry dichloromethane (2 cm^3) containing pyridine (2 cm^3) and *p*-dimethylaminopyridine (5 mg). An orange colour rapidly developed, but t.l.c. analysis using silica/chlororm:methanol:triethylamine (40:48:12) and silica/ethylacetate did not indicate the presence of any products, with the exception of some polymeric baseline material. No indole-2-carboxylic acid was observed.

Similarly, addition of the acid chloride, produced by Method 1, to a solution of harmalan and triethylamine in dichloromethane or benzene did not result in acylation, even after refluxing for several hours. In this case, the presence of a small amount of indole-2-carboxylic acid in the reaction mixture was observed. This was presumed to be the result of incomplete acid chloride formation in the preceding step.

The reaction of harmalan with ethyl indole-2-carboxylate.-Harmalan (100 mg, 0.5 mmol) was dissolved in dry benzene (8 cm^3) and triethylamine (0.5 cm^3) was added. Ethyl indole-2-carboxylate (103 mg, 0.5 mmol) was added and the resulting solution, after having been plafed under a positive pressure of nitrogen, was brought to reflux and maintained at that temperature for 15 h. The resultant precipitate was filtered off and analysed by ^1H n.m.r. spectroscopy. Only starting materials were evident. The mother liquors were evaporated to dryness and were similarly found to contain only starting material.

N-Methylindole (247).-Indole (4 g) was dissolved in acetone (100 cm^3) and to the colourless solution was added crushed potassium hydroxide (9.52 g). The suspension was stirred for 45 min and then methyliodide (4.2 cm^3) was added. After stirring for a further 45 min, toluene was introduced and the mixture was filtered. The filtrate was evaporated down to a mobile pale-yellow liquid, which was subsequently adsorbed onto silica and the resulting adsorbate was applied to the top of a silica column. Elution with 10% ethyl-acetate in petrol and collection of the pure product fractions, followed by co-evaporation, yielded the product as a viscous yellow liquid (3.81 g, 85%). ^1H n.m.r. $\delta(CDCl_3)$: 7.05-7.74 (4H, m, H-4, 5, 6 and 7), 6.82 [1H, d, (J= 6 Hz), H-2], 6.48 [1H, d, (J = 6 Hz), H-3], 3.36 (3H, s, $N-CH_3$); ν_{max} (liquid film) (cm^{-1}): 1515, 1465, 1320, 1245, 742.

1-Methylindole-2-carboxylic acid (248).-1-Methylindole (3.77 g, 0.029 mmol) was dissolved in freshly dried and distilled THF (40 cm^3) and the solution was cooled to -78° C. A 1.5 *M* solution of *n*-butyl-lithium in hexane (23 cm , 0.035 mmol) was added carefully, and the resulting mixture was allowed to warm to room temperature. After 1 h, the mixture was cooled to -78° C again and dried carbon dioxide gas was bubbled through until no further heating was observed. Evaporation of the colourless solution yielded a foaming gum which was partitioned between dilute sodium hydroxide and ether. The aqueous phase was acidified and extracted with chloroform; the organic layer was subseqently dried and evaporated to give 1-methylindole-2-carboxylic acid as a pale-cream solid (2.07 g, 41%). M.p. (ethanol) = 209.5-211° C. ^1H n.m.r. $\delta(d^6$-DMSO and $CDCl_3)$: 10.8 (1H, bs, CO_2H), 7.65 (1H, dd, H-4), 7-7.45 (4H, m, H-3, 5, 6 and 7), 4.05 (3H, s, $N-CH_3$); ν_{max} (cm^{-1}): 1690, 1520.

1-Methylene-2-[N'-methylindole-2'-carbonyl]-1,2,3,4-tetrahydro-β-carboline [(233), R = CH_3].-*N*-Methylindole-2-carboxylic acid (0.193 g, 1.1 mmol) was suspended in dry dichloromethane (8 cm^3) and two drops of dry dimethylformamide was added. Oxalyl chloride (0.1 cm^3, 0.146 g, 1.1 mmol) was introduced and the mixture was stirred at room

temperature. The acid gradually passed into solution; this was accompanied by the steady evolution of gas. When bubbling had finally ceased, the resulting acid chloride solution was added carefully, over 20 min, to an ice cold solution of harmalan (0.2 g, 1.09 mmol) in dry dichloromethane (3 cm^3) containing triethylamine (0.25 cm^3). The reaction mixture was stirred for 75 min; thin layer chromatographic analysis (25% ethylacetate in petrol/silica) after this time showing that all starting material had been consumed. Removal of the solvent under reduced pressure was followed by flash chromatography using the eluent system described above. Co-evaporation of the product fractions gave the title compound as a pale-yellow gum. Yield = 244 mg (65%). ^1H n.m.r. $\delta(CHCl_3)$: 8.75 (1H, bs, indole N-H), 7.1-7.7 (8H, m, aromatics), 6.65 (1H, s, H-3'), 4.65 and 5.05 [2 x 1H, 2 x d, (J = 2 Hz), examethylene protons], 4.25 [2H, t, (J = 5 Hz), CH_2-N], 3.75 (3H, s, N'-CH_3), 2.95 [2H, t, (J = 5 Hz), -CH_2-]; m/e E.I. eV (%): 341.1531 (M^+, 78), 326(32), 313(42), 185(48), 184(33), 175(24), 174(35), 173(54), 158(100), 130(28), 89(70). $C_{22}H_{19}N_3O$ requires: 341.1528; ν_{max} (cm^{-1}): 3480, 1640, 1405; λ_{max} (nm): 217, 305.

5-Methyl-5,8,9,14-tetrahydroindole[2,3-c]indolo[2,3-g]quinolizin-6-one [(234), R = CH_3].-The dienamide [(233), R = CH_3, 234 mg] synthesised previously was dissolved in analar grade benzene (500 cm^3) and the pale-yellow solution flushed with dry deoxygenated nitrogen for 35 min before irradiating with a 125 V medium pressure u.v. lamp.

After 15 h, during which the progress of the reaction was monitored by t.l.c. and u.v. analysis, the solution was evaporated down in the presence of silica. The resulting powder was applied to the top of a column of silica and subjected to flash chromatography with 45% ethyl-acetate in petrol as the eluent. The product fractions were combined, filtered and evaporated under reduced pressure to yield the title compound as a yellow solid (140 mg, 59.5%): m.p. > 300° C. ^1H n.m.r. $\delta[d^6$-DMSO/$(CD_3)_2CO]$: 11.35 (1H, bs, N-H), 7.75 [1H, d, (J = 7 Hz), H-1 or H-10], 6.7-7.5 (8H, m, aromatics), 4.25 [2H, t, (J = 6 Hz), CH -N], 4.00 (3H, s, N-CH_3), 2.80 [2H, t, (J = 6 Hz), -CH_2-];

ν_{max} (cm^{-1}): 3400, 1645, 1590; λ_{max} (nm): 228, 296, 315, 330(sh), 348, 390, m/e 339.1373 (M^+). $C_{22}H_{17}N_3O$ requires 339.1371.

The reaction of indole with phosgene.-Indole (2.92 g) was dissolved in dry toluene (40 cm^3) under an atmosphere of dry nitrogen and pyridine (2 cm^3, freshly distilled from potassium hydroxide) was added. A 12.5% solution (37.5 cm^3) of phosgene in toluene was introduced carefully and the solution was stirred at room temperature for 3 h, during which time a red-brown tar was deposited from solution. Absolute ethanol was then added until the mixture became homogeneous. T.l.c. analysis (silica/10% ethylacetate in petrol) showed one major product as well as starting material and polymeric substances. The solution was evaporated down and the residue chromatographed on silica using diethyl ether as the eluent. Co-evaporation of the product fractions yielded ethyl indole-3-carboxylate as an off-white solid (1.7 g, 36%) that was recrystallised from methanol; m.p. 124.5-125.5° C (lit.,[140] 124-125° C). M/e E.I. eV (%): 189 (M^+), 161, 144, 115, 99, 87, 79, 52 metastables at 137 (189 → 161), 109 (189 → 144), and 91.8 (144 → 115); ν_{max} (cm^{-1}): 3260, 1665, 1530. Because of the considerable degree of tar formation, this method was not considered to be suitable as a means of preparation of the indole-3-carbonyl derivative of harmalan.

1-Methylindole-3-carboxylic acid (250).-To a suspension of sodium hydride (1.06 g, 0.044 mmol) in dichloromethane (45 cm^3) and dimethylformamide (45 cm^3) under an atmosphere of dry nitrogen, was added indole-3-carboxylic acid (3.25 g, 0.02 mol). The resulting mixture was stirred for 100 min, by which time effervescence had ceased. Methyliodide (1.5 cm^3, 0.02 mmol) was then added; addition being accompanied by a renewed evolution of gas and a considerable increase in solution viscosity. Thorough mixing was achieved by agitating the reaction mixture in an ultrasonic bath for 45 min, after which time the contents of the reaction vessel were poured into dilute sodium hydroxide. The resulting solution was extracted with dichloromethane (3 x 100 cm^3) to remove the dimethylformamide, acidified

and then re-extracted with dichloromethane. The organic layer was subsequently washed with 2*M* hydrochloric acid (3 x 100 cm^3) and water (2 x 100 cm^3) before drying and evaporating down under reduced pressure. The residue was dried in a vacuum oven to yield the pure title compound as a colourless powder (2.6 g, 73.6%), m.p. (aqueous acetone): 212.5-213.5° C (lit.,[147] 214° C). ^{1}H n.m.r. $\delta(d^6$-DMSO): 7.75-7.95 (2H, m, H-2 and H-4), 6.9-7.5 (3H, m, H-5, 6 and 7), 3.7 (3H, s, N-CH_3).

15-Methyl-7,8,13,15-tetrahydroindolo[3,2-c]indolo[2,3-g]quinolizin-5-one [(236), R = CH_3].-1-Methylindole-3-carboxylic acid (1.0 g, 5.7 mmol) was suspended in dry dichloromethane (25 cm^3) and oxalyl-chloride (0.5 cm^3, 5.73 mmol) was added. The suspension was stirred for 75 min. until the acid had gone into solution and no further gas evolution was observed. The acid chloride solution was then added carefully over 15 min to a cooled solution of harmalan (1.0 g, 5.4 mmol) in dry triethylamine (3 cm^3) and dry dichloromethane (25 cm^3). After stirring in an ice bath for 90 min, the solution was evaporated down to a yellow-brown foam. No attempt was made to isolate the dienamide at this stage, as t.l.c. analysis (silica or alumina/ethylacetate) showed it to be unstable. Instead, the foam was dissolved in analar grade benzene and the mixture was filtered to remove triethylamine hydrochloride before being flushed thoroughly with dry deoxygenated nitrogen (1 h). The red solution was then subjected to irradiation with a 400 W medium pressure u.v. lamp for a total of 26 h. T.l.c. and u.v. analysis established that no further changes were taking place after this time and so the solution was evaporated down to give a red gum. Chromatography on alumina using ethylacetate as the eluent afforded the title compound as a canary-yellow solid. Yield = 280 mg, 15.2%: m.p. > 300° C. ^{1}H n.m.r. run at 140° C $\delta(d^6$-DMSO): 7.0-7.8 (9H, m, aromatics), 4.55 [2H, t, (*J* = 7 Hz), $-CH_2-N$], 3.92 (3H, s, N-CH_3), 3.16 [2H, t, (*J* = 7 Hz), $-CH_2-$]; m/e E.I. eV (%): 339.1376 (M^+, 100), 338(47), 337(26), 290(17), 245(24), 170(8). $C_{22}H_{17}N_3O$ requires 339.1371; ν_{max} (cm^{-1}): 3200, 1650, 1590, 1580, 1570, 750; λ_{max} (nm): 208, 242, 262, 281(sh), 295(sh), 353(sh), 374, 400.

2-Cinnamoyl-1-methylene-1,2,3,4-tetrahydro-β-carboline [(254), R = H].-Harmalan (1 g, 5.43 mmol) was dissolved in dry dichloromethane (11 cm^3) containing triethylamine (0.84 cm^3) and the resulting pale-yellow solutiln was cooled in an ice bath. A solution of cinnamoyl chloride (1 g, 6.0 mmol) in dichloromethane (5 cm^3) was added carefully and the reaction mixture was then stirred for 20 min, during which time a heavy precipitate formed. The precipitate was filtered off, washed sparingly with cold dichloromethane and then recrystallised from ethanol. Yield = 1.23 g (72%): m.p. = 200-201° C (dec). ^1H n.m.r. δ(d^6-DMSO): 11.34 (1H, s, indole N-H), 6.9-7.7 (11H, m, aromatic and cinnamoyl alkenic protons), 5.76 and 4.96 (2 x 1H, 2 z s, exomethylene protons), 4.15 [2H, t, (*J* = 6 Hz), $-\underline{CH_2}-N$], 2.89 [2H, t, (*J* = 6 Hz), $-CH_2-$]; m/e E.I. ev(%): 314 (M^+), 286 (M-CO), 285, 237 ($M-C_6H_5$), 223 ($M-PhCH_2$), 209, 184, 131 ($Ph-CH=CH-C\equiv\overset{+}{O}$), 103 ($PhCHCH^+$), 77 metastables at 81 (131 → 103), 57.5 (103 → 77) and 158.3 (314-223); ν_{max} (cm^{-1}): 3275, 1640, 1595, 980, 730; [Found: C, 79.98; H, 5.78; N, 8.98. $C_{21}H_{18}N_2O$ requires: C, 80.25; H, 5.73; N, 8.91]; λ_{max} (nm): 262, 306.

2,3,4,6,7,12-Hexahydro-4-oxo-2-phenylindolo[2,3-a]quinolizine (258).-2-Cinnamoyl-1-methylene-1,2,3,4-tetrahydro-β-carboline (300 mg, 0.95 mmol) was dissolved in analar grade methanol (500 cm^3) and the resulting solution was flushed thoroughly with dry deoxygenated nitrogen for 30 min. The solution was then irradiated with a 400 W medium pressure u.v. lamp for 30 h, during which time nitrogen was continuously bubbled through the solution. The progress of the reaction was monitored by u.v. analysis. (*N.B.* The Rf of the product by t.l.c. is identical to that of the starting material.)

The yellow solution was evaporated down to give a yellow-brown solid which was recrystallised from methanol to afford the title compound as a fine pale-cream solid (210 mg, 70%); m.p. > 300° C. ^1H n.m.r. δ(d^6-DMSO): 11.14 [1H, bs (exchangeable), N-H], 6.9-7.6 (4H, m, H-8, H-9, H-10 and H-11), 7.32 (5H, s, phenyl protons), 5.95 [1H, d, (*J* = 5 Hz), H-1],* 3.7-4.3 (3H, m, H-2 and $-CH_2-N$), 2.6-3.1 (4H, m, $-CH_2-$ and $CH_2-\overset{O}{\overset{\|}{C}}-N$); ν_{max} (cm^{-1}): 3270, 1625, 1425, 1400, 1055, 740; [Found: C, 80.04; H, 5.76; N, 8.75. $C_{21}H_{18}N_2O$ requires: C, 80.25; H, 5.73; N, 8.91]; λ_{max} (nm): 225, 311.

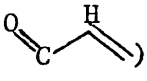
*Collapsed to a singlet when the group of signals at δ 3.7-4.3 was irradiated.

Ethyl-3-phenylbut-2-enoate (257).-Zinc turnings (40 g) were placed in a three-necked flask fitted with a mechanical stirrer. From a pressure equalising dropping funnel, and under a blanket of dry nitrogen, a solution of ethylbromoacetate (55.5 cm^3), acetophenone (73 cm^3) and dry ether (20 cm^3) in dry benzene (80 cm^3) was carefully added. The flask was warmed until initial reaction took place and thereafter the mixture was added at such a rate as to maintain gentle reflux. When addition was complete, the solution was heated at reflux for a period of 45 min before allowing to cool. To the cooled well stirred mixture was added 1 *M* sulphuric acid (200 cm^3) and when no solid zinc particles remained, the mixture was allowed to settle and the organic layer was removed. After washing with 1 *M* sulphuric acid (2 x 500 cm^3), water (2 x 50 cm^3), 2 *M* sodium carbonate (2 x 100 cm^3) and water (2 x 100 cm^3) again, the solution was dried and evaporated down to an oil. No attempt was made to purify and fully characterise the hydroxy ester. Instead, the crude oil was dissolved in benzene, phosphorus oxychloride (25 cm^3) added and the mixture was brought to reflux. After boiling for 40 min, the dark-red solution was allowed to cool to room temperature, whereupon it was washed successively with water (2 x 100 cm^3), saturated sodium bicarbonate solution (3 x 100 cm^3) and water (2 x 100 cm^3). The organic layer was dried over magnesium sulphate and evaporated down under reduced pressure to give a mobile oil which was subjected to vacuum distillation. The title compound was obtained as a pale-yellow oil (16.3 g, 17% from ethylbromoacetate), b.p. = 120° C (0.5 mmHg). ^1H n.m.r. $\delta(CDCl_3)$: 7.27 (5H, m, aromatics), 6.00 (1H, s, olefinic), 4.13 [2H, q, (*J* = 12 Hz), $-CH_2-$], 2.53 (3H, s, CH_3), 1.27 [3H, t, (*J* = 12 Hz), CH].

3-Phenylbut-2-enoic acid.-Ethyl-3-phenylbut-2-enoate (16.26 g) was added to 2 *M* sodium hydroxide (85 cm^3) and the mixture heated at 80-85° C for 3 h followed by boiling for 90 min. After allowing to cool to room temperature overnight, the solution was filtered and acidified to precipitate the *trans*-carboxylic acid as a colourless solid. The product was filtered, washed well with water and left to dry in a dessicator. Yield = 11 g (78%): m.p. = 97.5-99° C (lit.,[143]

98.5° C). ^{1}H n.m.r. δ($CDCl_3$): 10.55 [1H, bs (exchangeable), CO_2H], 7.42 (5H, m, aromatics), 6.12 [H, d, (J = 2 Hz), olefinic], 2.58 [3H, d, (J = 2 Hz), CH_3].

1-Methylene-2-[3'-phenylbut-2'-enoyl]-1,2,3,4-tetrahydro-β-carboline [(254), R = CH_3].-Potassium 3-phenylbut-2-enoate (0.86 g), formed by addition of finely powdered potassium hydroxide to a solution of 3-phenylbut-2-enoic acid in acetone followed by evaporation of the solvent under reduced pressure, was suspended in dry dichloromethane (15 cm^3) and oxalylchloride (0.37 cm^3, 4.35 mmol) was introduced. When the initial vigorous reaction had subsided, the reaction mixture was stirred for 1 h, after which time no further evolution of gas was observed.

Harmalan (0.8 g, 4.35 mmol) was dissolved in dry dichloromethane (50 cm^3) containing triethylamine (3 cm^3) and to the well stirred solution was added the acid chloride solution, dropwise over 1 h. When addition of the acid chloride solution was complete, the solution was stirred for a further 10 min before evaporating down under reduced pressure. The residue was chromatographed on neutral alumina using chloroform as the eluent and the product fractions were co-evaporated to yield a mobile oil which triturated to a canary-yellow solid in petrol (0.94 g, 66%). ^{1}H n.m.r. δ($CDCl_3$): 8.72 (1H, bs, exchangeable, indole N-H), 7.762 (9H, m, aromatics), 6.53 (1H, s, ), 5.35 (1H, s, exomethylene proton), 5.00 (1H, s, exomethylene proton), 4.2 [2H, t, (J = 6 Hz), $-CH_2-N$], 2.93 [2H, t, (J = 6 Hz), $-CH_2-$], 2.45 (3H, s, CH_3); m/e E.I. 70 eV (%): 328 (M^+, 100), 313(37), 300(32), 285(32), 223(52), 196(37), 184(42), 183(42), 145(60), 117(40), 115(47), 86(40); ν_{max} (cm^{-1}): 3270, 1638; λ_{max} (nm): 210, 226(sh), 257(sh), 306.

Attempted photocyclisation of 1-Methylene-2-[3'-phenylbut-2-enoyl]-1,2,3,4-tetrahydro-β-carboline [(254), R = CH_3].-The title compound (400 mg) was dissolved in dry analar grade methanol (350 cm^3) and the solution was flushed with dried deoxygenated nitrogen for 45 min before being irradiated with a 125 W medium pressure u.v. lamp for 30 h. T.l.c. and u.v. analysis during this time showed

that cyclisation was not taking place. This was confirmed when the solvent was removed under reduced pressure and a portion of the residue subjected to n.m.r. analysis. Some minor decomposition was observed.

Attempted thermal cyclisation of [(254), R = CH_3].-The above dienamide (40 mg) was placed in an n.m.r. tube and heated at 200° C in an oil bath for 30 min. Addition of deuterochloroform to the cooled, darkened solid and n.m.r. analysis of the solution showed that no cyclisation had taken place.

1-Methylene-2-cyclopropylcarbonyl-1,2,3,4-tetrahydro-β-carboline (261).-Harmalan (2.03 g, 0.011 mmol) was dissolved in dry dichloromethane (50 cm^3) and triethylamine (3 cm^3) introduced. The solution was cooled in an ice bath and cyclopropylcarbonyl chloride (1 cm^3, 0.011 mmol) was added dropwise over 30 min. The resulting solution was stirred at room temperature for 1 h, after which time t.l.c. analysis (silica/ethylacetate) indicated that all starting material had been consumed. Next, the reaction mixture was evaporated down in the presence of silica and the resulting powder was applied to the top of a silica column. Flash chromatography using 50% ethylacetate in petrol as the eluent and co-evaporation of the product fractions yielded the title compound as an unstable oil (400 mg) which slowly crystallised. The mixed fractions were re-chromatographed to yield a further 1.2 g of product. Total yield = 1.6 g (58%). ^1H n.m.r. $\delta(CDCl_3)$: 9.73 (1H, bs, indole N-H), 7.4-7.5 (2H, m, H-5 and H-8), 7.08 and 7.19 (2 x 1H, 2 x t, H-6 and H-7), 5.16 and 5.69 (2H, 2 x s, exomethylene protons), 4.16 [2H, t, (J = ∿6 Hz), $-CH_2-N$], 2.87 [2H, t, (J = ∿6 Hz), $-CH_2-$], 2.29 (1H, m, cyclopropyl α-proton), 1.1 and 0.76 (2 x 2H, 2 x m, cyclopropyl β-protons); m/e E.I. 10 eV (%): 252 (M^+, 100), 237(12), 223(12), 183(20); ν_{max} (cm^{-1}): 3450, 1632, 1448, 1410.

Photochemical reaction of the dienamide (261).-1-Methylene-2-cyclopropylcarbonyl-3,4-dihydro-β-carboline (200 mg) was dissolved in analar methanol (500 cm^3) and the resulting yellow solution was flushed with nitrogen for 40 min. The deoxygenated solution was then irradiated with a 400 W medium pressure u.v. lamp for 15 h.

Nitrogen was passed through the solution continuously during this time and the reaction was constantly monitored by t.l.c. analysis (silica/ethylacetate). Evaporation of the solution yielded a partially solidified oil which was triturated in ether to afford a solid. No starting material was present in the solid which streaked badly on t.l.c. and could not be resolved into components. N.m.r. analysis of the solid produced a spectrum too poorly resolved to be of any use and clearly a mixture of compounds was present. Treatment with hot ethylacetate divided the mixture into an ethylacetate soluble fraction A and an insoluble fraction B. Mass spectral analysis of A showed no peaks higher than m/e 185. Fraction B exhibited a peak at m/e 279. Further analysis was unproductive.

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